=> s (Lewis Y antigen) and (antibod?)

L4 206 (LEWIS Y ANTIGEN) AND (ANTIBOD?)

=> s l4 and fucosylated

L5 18 L4 AND FUCOSYLATED

=> s l4 and therapeutic

L6 55 L4 AND THERAPEUTIC

=> s l6 and cojugated

L7 0 L6 AND COJUGATED

=> dup rem l5 l6

PROCESSING COMPLETED FOR L5
PROCESSING COMPLETED FOR L6
L8 53 DUP REM L5 L6 (20 DUPLICATES REMOVED)

=> dup rem l8

PROCESSING COMPLETED FOR L8
L9 53 DUP REM L8 (0 DUPLICATES REMOVED)

=> d l9 1-53 bib ab

L9 ANSWER 1 OF 53 USPATFULL
AN 2001:33079 USPATFULL
TI Development of human monoclonal **antibodies** and uses thereof
IN Trakht, Ilya, New York, NY, United States
PA The Trustees of Columbia University in the City of New York, New York, NY, United States (U.S. corporation)
PI US 6197582 20010306
AI US 1998-40833 19980318 (9)
DT Utility
EXNAM Primary Examiner: Smith, Lynette R. F.; Assistant Examiner: Lee, Li
LREP White, John P.Cooper & Dunham LLP
CLMN Number of Claims: 9
ECL Exemplary Claim: 1
DRWN 6 Drawing Figure(s); 7 Drawing Page(s)
LN.CNT 1690
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The present invention provides a trioma cell which does not produce any **antibody** obtained by fusing a hetermomyeloma cell which does not produce any **antibody** with a human lymphoid cell, wherein the heteromyeloma cell is designated B6B11. The invention also provides a tetroma cell capable of producing a monoclonal **antibody** having specific binding affinity for an antigen obtained by fusing a trioma cell which does not produce any **antibody** with a human lymphoid cell capable of producing **antibody** having specific binding affinity for the antigen. The invention also provides methods for

generating trioma cells and tetroma cells, and the cells generated by the methods.

L9 ANSWER 2 OF 53 USPATFULL
AN 2000:12608 USPATFULL
TI Methods for determining the presence of carcinoma using the antigen binding region of monoclonal **antibody** BR96
IN Hellstrom, Ingegerd, Seattle, WA, United States
Hellstrom, Karl Erik, Seattle, WA, United States
Bruce, Kim Folger, Seattle, WA, United States
Schreiber, George J., Seattle, WA, United States
PA Bristol-Myers Squibb Company, Princeton, NJ, United States (U.S. corporation)
PI US 6020145 20000201
AI US 1994-333840 19941103 (8)
RLI Division of Ser. No. US 1993-77253, filed on 14 Jun 1993 which is a continuation-in-part of Ser. No. US 1993-57444, filed on 5 May 1993, now patented, Pat. No. US 5491088 which is a continuation of Ser. No. US 1990-544246, filed on 26 Jun 1990, now abandoned which is a continuation-in-part of Ser. No. US 1989-374947, filed on 30 Jun 1989, now abandoned
DT Utility
EXNAM Primary Examiner: Feisee, Lila; Assistant Examiner: Bansal, Geetha P.
LREP Merchant, Gould, Smith, Edell, Welter & Schmidt
CLMN Number of Claims: 4
ECL Exemplary Claim: 1,3
DRWN 76 Drawing Figure(s); 74 Drawing Page(s)
LN.CNT 5875
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The present invention relates to novel **antibodies**, **antibody** fragments and **antibody** conjugates and single-chain immunotoxins reactive with human carcinoma cells. More particularly, the **antibodies**, conjugates and single-chain immunotoxins of the invention include: a murine monoclonal **antibody**, BR96; a human/murine chimeric **antibody**, ChiBR96; a F(ab').sub.2 fragment of BR96; ChiBR96-PE, ChiBR96-LysPE40, ChiBR96 F(ab').sub.2 -LysPE40 and ChiBR96 Fab'-LysPE40 conjugates and recombinant BR96 sFv-PE40 immunotoxin. These molecules are reactive with a cell membrane antigen on the surface of human carcinomas. The BR96 **antibody** and its functional equivalents, displays a high degree of selectivity for carcinoma cells and possess the ability to mediate **antibody**-dependent cellular cytotoxicity and complement-dependent cytotoxicity activity. In addition, the **antibodies** of the invention internalize within the carcinoma cells to which they bind and are therefore particularly useful for therapeutic applications, for example, as the **antibody** component of **antibody**-drug or **antibody**-toxin conjugates. The **antibodies** also have a unique feature in that they are cytotoxic when used in the unmodified form, at specified concentrations.

L9 ANSWER 3 OF 53 USPATFULL
AN 2000:174092 USPATFULL
TI Dispersible '**antibody** compositions and methods for their preparation and use
IN Platz, Robert M., Half Moon Bay, CA, United States
Patton, John S., San Carlos, CA, United States
Foster, Linda C., Mountain View, CA, United States
Eljamal, Mohammed, Tripoli, Lebanon
PA Inhale Therapeutic Systems, Inc., San Carlos, CA, United States (U.S. corporation)
PI US 6165463 20001226

AI US 1999-323276 19990601 (9)
RLI Continuation of Ser. No. US 1997-951312, filed on 16 Oct 1997 which is a
continuation-in-part of Ser. No. US 423515
DT Utility
EXNAM Primary Examiner: Dees, Jose' G.; Assistant Examiner: Pryor, Alton
LREP Burns, Doane, Swecker & Mathis, L.L.P.
CLMN Number of Claims: 14
ECL Exemplary Claim: 1
DRWN 4 Drawing Figure(s); 4 Drawing Page(s)
LN.CNT 1015
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB This invention relates to dispersible **antibody** compositions and methods for preparing and using these compositions. In particular, the present invention relates to dry powder dispersible **antibody** compositions wherein **antibody** conformation is preserved. The compositions have good powder dispersibility and other desirable characteristics for pulmonary delivery of **therapeutic antibodies**.

L9 ANSWER 4 OF 53 USPATFULL
AN 2000:105706 USPATFULL
TI Multispecific chimeric receptors
IN Capon, Daniel J., Hillsborough, CA, United States
Smith, Douglas H., Foster City, CA, United States
Tian, Huan, Cupertino, CA, United States
Winslow, Genine A., Hayward, CA, United States
Siekevitz, Miriam, New York, NY, United States
PA Cell Genesys, Inc., Foster City, CA, United States (U.S. corporation)
PI US 6103521 20000815
AI US 1995-454098 19950530 (8)
RLI Continuation of Ser. No. US 1995-384033, filed on 6 Feb 1995, now abandoned
DT Utility
EXNAM Primary Examiner: Caputa, Anthony C.; Assistant Examiner: Pak, Michael
LREP Sughrue, Mion, Zinn, Macpeak & Seas, PLLC
CLMN Number of Claims: 47
ECL Exemplary Claim: 1
DRWN 3 Drawing Figure(s); 4 Drawing Page(s)
LN.CNT 2523
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Novel multispecific chimeric receptor DNA sequences, expression cassettes and vectors containing these sequences as well as cells containing the chimeric DNA and novel chimeric receptor proteins expressed from the sequences are provided in the present invention. The novel multispecific chimeric receptor DNA and amino acid sequences comprise at least three domains that do not naturally exist together: (1) a multispecific binding domain comprising at least two extracellular inducer-responsive clustering domains which serves to bind at least one specific inducer molecule, (2) a transmembrane domain, which crosses the plasma membrane, and (3) either a proliferation signaling domain that signals the cell to divide, or an effector function signaling domain which directs a host cell to perform its specialized function. Optionally, all the multispecific chimeric receptors may contain one or more intracellular inducer-responsive clustering domains attached to one or more of the cytoplasmic signaling domains or the transmembrane domain. The present invention also relates to novel hybrid multispecific chimeric receptors comprising at least one proliferation signaling domain and at least one effector function signaling domain together on the multispecific receptor molecule. The present invention further

relates to **therapeutic** methods and strategies that employ the cells expressing these novel chimeric receptors for the treatment of cancer, infectious disease and autoimmune disease which may have greater **therapeutic** benefit over a combination of drug therapies.

L9 ANSWER 5 OF 53 USPATFULL
AN 2000:12431 USPATFULL
TI Dispersible **antibody** compositions and methods for their preparation and use
IN Platz, Robert M., Half Moon Bay, CA, United States
Patton, John S., San Carlos, CA, United States
Foster, Linda C., Mountain View, CA, United States
Eljamal, Mohammed, Tripoli, Lebanon
PA Inhale Therapeutic Systems, Inc., San Carlos, CA, United States (U.S. corporation)
PI US 6019968 20000201
AI US 1997-951312 19971016 (8)
RLI Continuation-in-part of Ser. No. US 1995-423515, filed on 14 Apr 1995 And Ser. No. WO 1996-US5070, filed on 12 Apr 1996
DT Utility
EXNAM Primary Examiner: Dees, Jose' G.; Assistant Examiner: Pryor, Alton
LREP Burns, Doane, Swecker & Mathis, L.L.P.
CLMN Number of Claims: 13
ECL Exemplary Claim: 1
DRWN 4 Drawing Figure(s); 4 Drawing Page(s)
LN.CNT 1012
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB This invention relates to dispersible **antibody** compositions and methods for preparing and using these compositions. In particular, the present invention relates to dry powder dispersible **antibody** compositions wherein **antibody** conformation is preserved. The compositions have good powder dispersibility and other desirable characteristics for pulmonary delivery of **therapeutic antibodies**.

L9 ANSWER 6 OF 53 MEDLINE
AN 2000447182 MEDLINE
DN 20452383
TI **Therapeutic** efficacy of anti-Lewis(y) humanized 3S193 radioimmunotherapy in a breast cancer model: enhanced activity when combined with taxol chemotherapy.
AU Clarke K; Lee F T; Brechbiel M W; Smyth F E; Old L J; Scott A M
CS Tumour Targeting Program, Ludwig Institute for Cancer Research, Melbourne Branch, Austin and Repatriation Medical Centre, Victoria, Australia.
SO CLINICAL CANCER RESEARCH, (2000 Sep) 6 (9) 3621-8.
Journal code: C2H. ISSN: 1078-0432.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200102
AB Monoclonal **antibody** therapy may provide new treatment options in the management of metastatic breast cancer by selectively targeting tumors and producing a **therapeutic** effect, by delivering radiation or other toxins directly to tumor cells, or by producing an intrinsic immune inflammatory response. The effect of 131I-labeled humanized anti-Lewis(y) monoclonal **antibody** 3S193 (hu3S193) was compared with that of placebo and radiolabeled huA33 control **antibody** in a series of radioimmunotherapy experiments in a MCF-7 xenografted BALB/c nude mouse breast cancer model. The maximum tolerated dose of 131I-labeled **antibody** occurred at 200 microCi/mouse, at which dose level three of six mice that received 131I-hu3S193 showed significant tumor growth

inhibition in contrast to no responses in the comparable 131I-huA33 control treatment arm. Breast cancer is an ideal model to test the efficacy of combined modalities given its known sensitivity to both radiotherapy and chemotherapy. The synergy between radioimmunotherapy and chemotherapy was therefore also explored using a combination of 131I-labeled hu3S193 **antibody** and Taxol using subtherapeutic doses of each agent. The combination of Taxol and 100 microCi of 131I-hu3S193 produced significant tumor inhibition in 80% of mice, whereas no responses were seen with either treatment modality alone or the combination of Taxol and 131I-huA33. These results support a potential **therapeutic** role of radiolabeled hu3S193 in the treatment of breast cancer, including combination therapy with Taxol, and warrants further investigation of this promising new agent.

L9 ANSWER 7 OF 53 MEDLINE
AN 2000322688 MEDLINE
DN 20322688
TI Construction, production, and characterization of humanized anti-Lewis Y monoclonal **antibody** 3S193 for targeted immunotherapy of solid tumors.
AU Scott A M; Geleick D; Rubira M; Clarke K; Nice E C; Smyth F E; Stockert E;
Richards E C; Carr F J; Harris W J; Armour K L; Rood J; Kypridis A; Kronina V; Murphy R; Lee F T; Liu Z; Kitamura K; Ritter G; Laughton K; Hoffman E; Burgess A W; Old L J
CS Ludwig Institute for Cancer Research, Melbourne Tumour Biology Branch, Victoria, Australia.
SO CANCER RESEARCH, (2000 Jun 15) 60 (12) 3254-61.
Journal code: CNF. ISSN: 0008-5472.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 200009
EW 20000904
AB The Lewis Y (Ley) antigen is a blood group-related antigen that is expressed in a high proportion of epithelial cancers (including breast, colon, ovary, and lung cancer) and is an attractive target for monoclonal **antibody**-directed therapy. The murine monoclonal 3S193 (IgG3) was generated in BALB/c mice by immunization with Ley-expressing cells of the MCF-7 breast carcinoma cell-line. The murine 3S193 showed high specificity for Ley in ELISA tests with synthetic Ley and Ley-containing glycoproteins and glycolipids and also reacted strongly in rosetting assays and cytotoxic tests with Ley-expressing cells. We generated a humanized form of the murine 3S193 **antibody** by linking cDNA sequences encoding the variable region of murine 3S913 with frameworks of the human KOL heavy chain and REI K chain. The genes for the humanized 3S193 monoclonal **antibody** IgG1 were transfected into mouse myeloma NS0 cells and cloned for the establishment of high **antibody**-producing colonies. Humanized 3S193 **antibody** was subsequently produced through in vitro culture and under good manufacturing practice conditions using hollow-fiber bioreactors. The purified humanized 3S193 (hu3S193) was subsequently characterized and validated for use in preliminary immunotherapy investigations. hu3S193 reacted specifically with Ley antigen, with similar avidity to the murine form. hu3S193 demonstrated potent immune effector function, with higher **antibody**-dependent cell-mediated cytotoxicity than its murine counterpart and potent complement-dependent cytotoxicity (ED50, 1.0 microg/ml). The in vivo immunotherapeutic potential of hu3S193 was assessed in a human breast

xenograft model using MCF-7, Ley-positive cells. Six i.v. doses of up to 1
mg of hu3S193 were administered to animals bearing established tumors (120-130 mm3) with no significant effect on tumor growth. In contrast, in an MCF-7 xenograft preventive model, a 1-mg hu3S193 dosage schedule was able to significantly slow tumor growth compared with placebo and isotype-matched control IgG1 **antibody**. hu3S193 has promise for immunotherapy of Ley-positive tumors and is currently entering Phase I clinical trials.

L9 ANSWER 8 OF 53 MEDLINE
AN 2000183955 MEDLINE
DN 20183955
TI Polyclonal **antibodies** from patients immunized with a globo H-keyhole limpet hemocyanin vaccine: isolation, quantification, and characterization of immune responses by using totally synthetic immobilized tumor antigens.
AU Wang Z G; Williams L J; Zhang X F; Zatorski A; Kudryashov V; Ragupathi G; Spassova M; Bornmann W; Slovin S F; Scher H I; Livingston P O; Lloyd K O; Danishefsky S J
CS Division of Genitourinary Oncology, Department of Medicine, and Laboratory of Bio-organic Chemistry, Memorial Sloan-Kettering Cancer Center, New York, NY 10021, USA.
NC AI-16943 (NIAID)
CA-28824 (NCI)
CA-71506 (NCI)
+
SO PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (2000 Mar 14) 97 (6) 2719-24.
Journal code: PV3. ISSN: 0027-8424.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 200006
EW 20000605
AB We have previously reported on a carbohydrate-based vaccine program for immunotherapy in cancer patients. One such vaccine, based on the globo H antigen conjugated to the protein keyhole limpet hemocyanin (KLH), has been in clinical evaluation. Although this and other carbohydrate vaccines have been shown to induce **antibody** responses, there are currently no quantitative data on the **antibody** levels achieved in immunized patients by these or other anti-cancer vaccines. We report herein an efficient route to complex synthetic oligosaccharides attached to an affinity matrix for identifying and isolating **antibodies** elicited against such a carbohydrate-based vaccine in humans. Pre- and postvaccination profiles from serum samples of patients immunized with globo H-KLH were compared. All anti-globo H **antibody** activity was efficiently separated from other serum constituents. The isolated **antibodies** were readily quantified, and their specificities were analyzed. Since no comparable data were available on **antibodies** resulting from the vaccination of other cancer patients, we compared the observed levels with those quoted in studies with bacterial polysaccharide vaccines that had been quantified. Remarkably, cancer patients immunized with globo H-KLH produce anti-globo H **antibody** levels often exceeding those formed by immunization with bacterial polysaccharides. In addition, substantial quantities of both IgG and IgM **antibodies** were elicited, clearly indicating a class switch to IgG. Taken together, these analyses serve to clarify several aspects of the immune response to the vaccine and give several new insights to the carbohydrate-based vaccination strategy. Furthermore, **antibodies** so isolated could

well have applications in clinical therapy.

L9 ANSWER 9 OF 53 MEDLINE
AN 2000291215 MEDLINE
DN 20291215
TI Phase I trial of the anti-Lewis Y drug immunoconjugate BR96-doxorubicin in patients with lewis Y-expressing epithelial tumors.
AU Saleh M N; Sugarman S; Murray J; Ostroff J B; Healey D; Jones D; Daniel C R; LeBherz D; Brewer H; Onetto N; LoBuglio A F
CS Department of Medicine, Division of Hematology/Oncology, Comprehensive Cancer Center, University of Alabama at Birmingham, 35294-3300, USA.. mansoor.saleh@ccc.uab.edu
SO JOURNAL OF CLINICAL ONCOLOGY, (2000 Jun) 18 (11) 2282-92.
Journal code: JCO. ISSN: 0732-183X.
CY United States
DT (CLINICAL TRIAL)
(CLINICAL TRIAL, PHASE I)
Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 200009
EW 20000902
AB PURPOSE: We conducted a phase I clinical trial of BR96-Doxorubicin (BR96-Dox), a chimeric anti-Lewis Y (Le(Y)) monoclonal **antibody** conjugated to doxorubicin, in patients whose tumors expressed the Le(Y) antigen. The study aimed to determine the toxicity, maximum-tolerated dose, pharmacokinetics, and immunogenicity of BR96-Dox. PATIENTS AND METHODS: This was a phase I dose escalation study. BR96-Dox was initially administered alone as a 2-hour infusion every 3 weeks. The occurrence of gastrointestinal (GI) toxicity necessitated the administration of BR96-Dox as a continuous infusion over 24 hours and use of antiemetics and antigastritis premedication. Patients experiencing severe GI toxicity underwent GI endoscopy. All patients underwent restaging after two cycles. RESULTS: A total of 66 patients predominantly with metastatic colon and breast cancer were enrolled onto the study. The most common side effects were GI toxicity, fever, and elevation of pancreatic lipase. At higher doses, BR96-Dox was associated with nausea, vomiting, and endoscopically documented exudative gastritis of the upper GI tract, which was dose-limiting at a maximum dose of 875 mg/m(2) (doxorubicin equivalent, 25 mg/m(2)) administered every 3 weeks. Toxicity was reversible and generally of short duration. Premedication with the antiemetic Kytril (granisetron hydrochloride; SmithKline Beecham, Philadelphia, PA), the antacid omeprazole, and dexamethasone was most effective in ameliorating GI toxicity. A dose of 700 mg/m(2) BR96-Dox (doxorubicin equivalent, 19 mg/m(2)) every 3 weeks was determined to be the optimal phase II dose when administered with antiemetic and antigastritis prophylaxis. BR96-Dox deposition on tumor tissue was documented immunohistochemically and by confocal microscopy. At the 550-mg/m(2) dose, the half-life (mean +/- SD) of BR96 and doxorubicin was 300 +/- 95 hours and 43 +/- 4 hours, respectively. BR96-Dox elicited a weak immune response in 37% of patients. Objective clinical responses were seen in two patients. CONCLUSION: BR96-Dox provides a unique strategy to deliver doxorubicin to Le(Y)-expressing tumor and was well tolerated at doses of 700 mg/m(2) every 3 weeks. BR96-Dox was not associated with the typical side-effect profile of native doxorubicin and can potentially deliver high doses of doxorubicin to antigen-expressing tumors. A phase II study in doxorubicin-sensitive tumors is warranted.

L9 ANSWER 10 OF 53 MEDLINE
AN 2000410717 MEDLINE
DN 20273337
TI Imaging and phase I study of 111In- and 90Y-labeled anti-LewisY monoclonal **antibody** B3.
AU Pai-Scherf L H; Carrasquillo J A; Paik C; Gansow O; Whatley M; Pearson D; Webber K; Hamilton M; Allegra C; Brechbiel M; Willingham M C; Pastan I
CS Laboratory of Molecular Biology, National Cancer Institute, NIH, Bethesda, Maryland 20892-4255, USA.
SO CLINICAL CANCER RESEARCH, (2000 May) 6 (5) 1720-30.
Journal code: C2H. ISSN: 1078-0432.
CY United States
DT (CLINICAL TRIAL)
(CLINICAL TRIAL, PHASE I)
Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200011
EW 20001101
AB B3 is a murine monoclonal **antibody** (mAb) that recognizes a LewisY carbohydrate antigen present on the surface of many carcinomas. An imaging and Phase I trial was performed to study the ability of 111In-mAb B3 to image known metastasis and determine the maximum tolerated dose (MTD), dose-limiting toxicity (DLT), kinetics, and biodistribution of 90Y-mAb B3. Patients (n = 26) with advanced epithelial tumors that express the LewisY antigen were entered. All patients received 5 mCi of 111In-mAb B3 for imaging. 90Y-mAb B3 doses were escalated from 5 to 25 mCi in 5-mCi increments. 111In-mAb B3 and 90Y-mAb B3 were coadministered over a 1-h infusion. Definite tumor imaging was observed in 20 of 26 patients. Sites imaged included lung, liver, bone, and soft tissues. The MTD of 90Y-mAb B3 was determined to be 20 mCi. The DLTs were neutropenia and thrombocytopenia. Tumor doses ranged from 7.7 to 65.1 rad/mCi. 111In- and 90Y-mAb B3 serum pharmacokinetics (n = 23) were found to be similar. The amount of B3 administered (5, 10, and 50 mg) did not alter the pharmacokinetics. Bone marrow biopsies (n = 23) showed 0.0038+/-0.0016% of injected dose/gram for 111In-mAb B3 compared to 0.0046+/-0.0017% of injected dose/gram for 90Y-mAb B3 (P = 0.009). When given to patients with carcinomas that express the LewisY antigen, 111In-mAb B3 demonstrated good tumor localization. The MTD of 90Y-mAb B3 is 20 mCi, with myelosuppression as the DLT. Higher doses of radioactivity need to be delivered to achieve an antitumor effect. Humanized mAb B3 is being developed for evaluation in radioimmunotherapy. A clinical trial to explore the use of higher doses of 90Y-mAb B3 with autologous stem cell support is planned.

L9 ANSWER 11 OF 53 BIOSIS COPYRIGHT 2001 BIOSIS
AN 2000:355796 BIOSIS
DN PREV200000355796
TI Influence of immunogenicity on the pharmacokinetics of BMS-191352, a Pseudomonas exotoxin immunoconjugate, in rats and dogs.
AU Damle, Bharat (1); Tay, Lee; Comèreski, Charles; Warner, William; Kaul, Sanjeev
CS (1) Metabolism and Pharmacokinetics, Bristol-Myers Squibb Pharmaceutical Research Institute, Princeton, NJ, 08543-4000 USA

SO Journal of Pharmacy and Pharmacology, (June, 2000) Vol. 52, No. 6, pp. 671-678. print.
ISSN: 0022-3573.
DT Article
LA English
SL English
AB BMS-191352 is an immunotoxin construct of modified Pseudomonas exotoxin conjugated to a fragment of the BR96 monoclonal **antibody**. We have investigated the potential for immunogenicity of BMS-191352 and its influence on the pharmacokinetics in rats and dogs. BMS-191352 was administered intravenously at doses of 0.75, 1.5, and 3 mg m-2 once every two days for a total of five doses in rats, and 1.2, 2.4, and 4.8 mg m-2 once every three days for a total of five doses in dogs. Blood samples were collected on days 1 and 9 in rats, and on days 1, 7, and 13 in dogs to monitor pharmacokinetics and anti-BMS-191352 immune response. Plasma concentrations of BMS-191352 and serum anti-BMS-191352 **antibody** titre were determined using ELISA assays. Pharmacokinetics were assessed using a non-compartmental method. Anti-BMS-191352 **antibodies** were not observed in rats within the drug administration interval. In all dogs, except one, markedly higher anti-BMS-191352 **antibody** titres were observed on day 13 compared with days 1 and 7, and its magnitude was independent of BMS-191352 dose. The single dose kinetics of BMS-191352 in rats and dogs were linear and the drug exposures were generally dose proportional. Mean half-life, total body clearance, and volume of distribution were 1.74 h, 3.35 mL min-1 m-2, and 0.27 L m-2 in rats, respectively, and 4.27 h, 6.28 mL min-1 m-2, 1.19 L m-2 in dogs, respectively. The multiple-dose (day 9) kinetics in rats were similar to the single-dose kinetics. In dogs, the disposition of BMS-191352 on day 7 was similar to that on day 1; however, there was a precipitous reduction in the systemic drug exposure (by 5- to 110-fold) and marked increase in drug clearance on day 13. These changes in the kinetics of BMS-191352 were attributed to the generation of anti-BMS-191352 **antibodies**. In the one dog that did not develop anti-BMS-191352 **antibodies**, the pharmacokinetics were unchanged. The pharmacokinetics of BMS-191352 may be perturbed due to an immune response thus restricting the **therapeutic** utility of the immunotoxin.

L9 ANSWER 12 OF 53 MEDLINE
AN 2000141547 MEDLINE
DN 20141547
TI Analysis of glycoproteins in cancers and normal tissues reactive with monoclonal **antibodies** B3 and B1.
AU Mariano A; Di Carlo A; Pastan I; Macchia V
CS Dipartimento di Biologia e Patologia Cellulare e Molecolare, Universita di Napoli, 80131 Napoli, Italy.
SO INTERNATIONAL JOURNAL OF ONCOLOGY, (2000 Mar) 16 (3) 549-53.
Journal code: CX5. ISSN: 1019-6439.
CY Greece
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200005
EW 20000503
AB In this study we show by immunoblotting that B1 and B3, two newly isolated monoclonal **antibodies**, react with a variety of glycoproteins with different molecular weights expressed in stomach, pancreas, colorectal and breast cancers. The pattern of reactivity differed among cancers arising in different tissues, although no correlation has been observed with the histopathological characteristics of the lesion analysed. MAb B3 and MAb B1, have a limited reactivity with peritumoral

tissues, whereas react very strongly with metastatic lesion. Because of the limited reactivity of these **antibodies** with normal tissue, MAbs B3 and B1, armed with toxin in the form of recombinant immunotoxins, can be useful in treating certain kinds of cancer such as metastatic lesions. However, until current clinical trials are completed, we will not know if they will be helpful in cancer treatment.

L9 ANSWER 13 OF 53 MEDLINE
AN 2000491401 MEDLINE
DN 20496567
TI A bispecific single-chain **antibody** directed against EpCAM/CD3 in combination with the cytokines interferon alpha and interleukin-2 efficiently retargets T and CD3+CD56+ natural-killer-like T lymphocytes to EpCAM-expressing tumor cells.
AU Flieger D; Kufer P; Beier I; Sauerbruch T; Schmidt-Wolf I G
CS Medizinische Klinik und Poliklinik I, Allgemeine Innere Medizin, Universitat Bonn, Germany.. D.Flieger@uni-bonn.de
SO CANCER IMMUNOLOGY, IMMUNOTHERAPY, (2000 Oct) 49 (8) 441-8. Journal code: CN3. ISSN: 0340-7004.
CY GERMANY: Germany, Federal Republic of
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200011
AB Cytokine-induced killer cells (CIK), generated in vitro from peripheral blood mononuclear cells (PBMC) by addition of interferon gamma (IFNgamma), interleukin-2 (IL-2), IL-1 and a monoclonal **antibody** (mAb) against CD3, are highly efficient cytotoxic effector cells with the CD3+CD56+ phenotype. In this study, we evaluated whether the cytotoxicity of these natural-killer-like T lymphocytes against the colorectal tumor cell line HT29 can be enhanced by the addition of a bispecific single-chain **antibody** (bsAb) directed against EpCAM/CD3. For determination of bsAb-redirected cellular cytotoxicity we used a new flow-cytometric assay, which directly counts viable tumor cells and can assess long-term cytotoxicity. We found that this bsAb induced distinct cytotoxicity at a concentration above 100 ng/ml with both PBMC and CIK at an effector-to-target cell ratio as low as 1:1. CIK cells revealed higher bsAb-redirected cytotoxicity than PBMC. Cellular cytotoxicity appeared after 24 h whereas PBMC showed the highest bsAb-redirected cytotoxicity after 72 h. The addition of the cytokines IL-2 and IFNalpha but not granulocyte/macrophage-colony-stimulating factor enhanced bsAb-redirected cytotoxicity of both PBMC and CIK. When the bsAb was combined with the murine mAb BR55-2, which recognizes the **Lewis(Y) antigen**, bsAb-redirected cytotoxicity was partly augmented, whereas murine mAb 17-1A, which binds to EpCAM as well, slightly suppressed bsAb-redirected cytotoxicity induced by the bsAb. We conclude that CIK generated in vitro or in vivo combined with this new EpCAM/CD3 bsAb and the cytokine IL-2 should be evaluated for the treatment of EpCAM-expressing tumors.

L9 ANSWER 14 OF 53 MEDLINE
AN 2000321432 MEDLINE
DN 20321432
TI Immunization of ovarian cancer patients with a synthetic Lewis(y)-protein conjugate vaccine: a phase 1 trial.
AU Sabbatini P J; Kudryashov V; Ragupathi G; Danishefsky S J; Livingston P O; Bornmann W; Spassova M; Zatorski A; Spriggs D; Aghajanian C; Soignet S; Peyton M; O'Flaherty C; Curtin J; Lloyd K O
CS Department of Medicine, Division of Developmental Chemotherapy, Memorial Hospital, New York, New York, USA.

NC CA71506 (NCI)
CA52477 (NCI)
AI16943 (NIAID)
+
SO INTERNATIONAL JOURNAL OF CANCER, (2000 Jul 1) 87 (1) 79-85.
Journal code: GQU. ISSN: 0020-7136.
CY United States
DT (CLINICAL TRIAL)
(CLINICAL TRIAL, PHASE I)
Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 200009
EW 20000903
AB As the initial step in developing carbohydrate-based vaccines for the treatment of ovarian cancer patients in an adjuvant setting, 25 patients were immunized with a Lewis(y) pentasaccharide (Le(y))-keyhole limpet hemocyanin (KLH)-conjugate vaccine together with the immunological adjuvant QS-21. Four different doses of the vaccine, containing 3, 10, 30, and 60 microg of carbohydrate were administered s.c. at 0, 1, 2, 3, 7, and 19 weeks to groups of 6 patients. Sera taken from the patients at regular intervals were assayed by ELISA for reactivity with naturally occurring forms of Le(y) (Le(y)-ceramide and Le(y) mucin) and by flow cytometry and a complement-dependent cytoxicity assay for reactivity with Le(y)-expressing tumor cells. The majority of the patients (16/24) produced anti-Le(y) **antibodies** as assessed by ELISA, and a proportion of these had strong anti-tumor cell reactivity as assessed by flow cytometry and complement-dependent cytotoxicity. One serum, analyzed in detail, was shown to react with glycolipids but not with glycoproteins or mucins expressed by ovarian cancer cell line OVCAR-3. The vaccine was well tolerated and no gastrointestinal, hematologic, renal, or hepatic toxicity related to the vaccine was observed. On the basis of this study, Le(y)-KLH should be a suitable component for a polyvalent vaccine under consideration for the therapy of epithelial cancers. Copyright 2000 Wiley-Liss, Inc.

L9 ANSWER 15 OF 53 USPATFULL
AN 1999:141303 USPATFULL
TI **Antibodies** reactive with human carcinomas
IN Hellstrom, Ingegerd, Seattle, WA, United States
Hellstrom, Karl Erik, Seattle, WA, United States
Bruce, Kim Folger, Seattle, WA, United States
Schreiber, George J., Redmond, WA, United States
Siegall, Clay, Edmonds, WA, United States
McAndrew, Stephen, Newtown, PA, United States
PA Bristol-Myers Squibb Company, Princeton, NJ, United States (U.S. corporation)
PI US 5980896 19991109
AI US 1993-77253 19930614 (8)
RLI Continuation-in-part of Ser. No. US 1993-57444, filed on 5 May 1993, now patented, Pat. No. US 5491088 And Ser. No. US 1992-892501, filed on 1 Jun 1992, now abandoned which is a continuation-in-part of Ser. No. US 1990-544246, filed on 26 Jun 1990, now abandoned which is a continuation-in-part of Ser. No. US 1989-374947, filed on 30 Jun 1989, now abandoned , said Ser. No. US 1993-57444, filed on 5 May 1993, now patented, Pat. No. US 5491088 which is a continuation of Ser. No. US 544246
DT Utility
EXNAM Primary Examiner: Feisee, Lila; Assistant Examiner: Bansal, Geetha P.
LREP Merchant, Gould, Smith, Edell, Welter & Schmidt
CLMN Number of Claims: 35

ECL Exemplary Claim: 1,16,34
DRWN 76 Drawing Figure(s); 74 Drawing Page(s)
LN.CNT 5987
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The present invention relates to novel **antibodies**, **antibody** fragments and **antibody** conjugates and single-chain immunotoxins reactive with human carcinoma cells. More particularly, the **antibodies**, conjugates and single-chain immunotoxins of the invention include: a murine monoclonal **antibody**, BR96; a human/murine chimeric **antibody**, ChiBR96; a F(ab').sub.2 fragment of BR96; ChiBR96-PE, ChiBR96-LysPE40, ChiBR96 F(ab').sub.2 -LysPE40 and ChiBR96 Fab'-LysPE40 conjugates and recombinant BR96 sFv-PE40 immunotoxin. These molecules are reactive with a cell membrane antigen on the surface of human carcinomas. The BR96 **antibody** and its functional equivalents, displays a high degree of selectivity for carcinoma cells and possess the ability to mediate **antibody**-dependent cellular cytotoxicity and complement-dependent cytotoxicity activity. In addition, the **antibodies** of the invention internalize within the carcinoma cells to which they bind and are therefore particularly useful for therapeutic applications, for example, as the **antibody** component of **antibody**-drug or **antibody**-toxin conjugates. The **antibodies** also have a unique feature in that they are cytotoxic when used in the unmodified form, at specified concentrations.

L9 ANSWER 16 OF 53 USPATFULL
AN 1999:89024 USPATFULL
TI Cloning and expression of a gene encoding bryodin 1 from Bryonia dioica
IN Siegall, Clay B., Edmonds, WA, United States
PA Bristol-Myers Squibb Company, New York, NY, United States (U.S. corporation)
PI US 5932447 19990803
AI US 1996-597731 19960207 (8)
RLI Division of Ser. No. US 1994-245754, filed on 17 May 1994, now patented, Pat. No. US 5541110
DT Utility
EXNAM Primary Examiner: Eisenschenk, Frank C.; Assistant Examiner: Nolan, Patrick
LREP Poor, Brian W.
CLMN Number of Claims: 10
ECL Exemplary Claim: 1
DRWN 14 Drawing Figure(s); 10 Drawing Page(s)
LN.CNT 1094
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The molecular cloning and expression of biologically active ribosome-inactivating protein bryodin 1 are described. A complete amino acid and oligonucleotide sequence encoding bryodin 1 are also described.
Further, plasmids, expression vectors comprising a nucleotide sequence encoding bryodin 1 and transformed host cells are described. Isolation and characterization of the nucleotide sequence for bryodin 1 enables the recombinant production of large amount of bryodin 1 for use in vitro or in vivo directly or as ligand/toxin conjugates or fusion proteins. These compositions can be used to selectively kill undesired cells such as cancer cells, infected cells, bacteria and the like.

L9 ANSWER 17 OF 53 USPATFULL
AN 1999:18719 USPATFULL
TI **Antibody** conjugates reactive with human carcinomas
IN Hellstrom, Ingegerg, Seattle, WA, United States

Hellstrom, Karl Erik, Seattle, WA, United States
Bruce, Kim Folger, Seattle, WA, United States
Schreiber, George J., Seattle, WA, United States
PA Bristol-Myers Squibb Company, New York, NY, United States (U.S. corporation)
PI US 5869045 19990209
AI US 1995-459354 19950602 (8)
RLI Division of Ser. No. US 1993-77253, filed on 14 Jun 1993 which is a continuation-in-part of Ser. No. US 1993-57444, filed on 5 May 1993, now patented, Pat. No. US 5491088 which is a continuation of Ser. No. US 1990-544246, filed on 26 Jun 1990, now abandoned which is a continuation-in-part of Ser. No. US 1989-374947, filed on 30 Jun 1989, now abandoned
DT Utility
EXNAM Primary Examiner: Feisee, Lila; Assistant Examiner: Ungar, Susan
LREP Merchant, Gould, Smith, Welter and Schmidt
CLMN Number of Claims: 7
ECL Exemplary Claim: 1
DRWN 75 Drawing Figure(s); 74 Drawing Page(s)
LN.CNT 5935
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The present invention relates to novel **antibodies**, **antibody** fragments and **antibody** conjugates and single-chain immunotoxins reactive with human carcinoma cells. More particularly, the **antibodies**, conjugates and single-chain immunotoxins of the invention include: a murine monoclonal **antibody**, BR96; a human/murine chimeric **antibody**, ChiBR96; a F(ab').sub.2 fragment of BR96; ChiBR96-PE, ChiBR96-LysPE40, ChiBR96 F(ab').sub.2 -LysPE40 and ChiBR96 Fab'-LysPE40 conjugates and recombinant BR96 sFv-PE40 immunotoxin. These molecules are reactive with a cell membrane antigen on the surface of human carcinomas. The BR96 **antibody** and its functional equivalents, displays a high degree of selectivity for carcinoma cells and possess the ability to mediate **antibody**-dependent cellular cytotoxicity and complement-dependent cytotoxicity activity. In addition, the **antibodies** of the invention internalize within the carcinoma cells to which they bind and are therefore particularly useful for therapeutic applications, for example, as the **antibody** component of **antibody**-drug or **antibody**-toxin conjugates. The **antibodies** also have a unique feature in that they are cytotoxic when used in the unmodified form, at specified concentrations.

L9 ANSWER 18 OF 53 USPATFULL
AN 1999:24286 USPATFULL
TI Recombinant human anti-Lewis Y **antibodies**
IN Armour, Kathryn Lesley, Aberdeen, Great Britain
Carr, Francis Joseph, Balmedie, Great Britain
Old, Lloyd J., New York, NY, United States
Stockert, Elisabeth, New York, NY, United States
Welt, Sydney, New York, NY, United States
Kitamura, Kunio, New York, NY, United States
Garin-Chesa, Pilar, Biberach, Germany, Federal Republic of
PA Memorial Sloan Kettering Cancer Center, New York, NY, United States (U.S. corporation)
PI US 5874060 19990223
AI US 1997-859649 19970520 (8)
RLI Division of Ser. No. US 1994-207861, filed on 8 Mar 1994
DT Utility
EXNAM Primary Examiner: Feisee, Lila; Assistant Examiner: Ungar, Susan
LREP Fulbright & Jaworski, LLP.
CLMN Number of Claims: 7

ECL Exemplary Claim: 1
DRWN 4 Drawing Figure(s); 4 Drawing Page(s)
LN.CNT 1164
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The invention provides for the production of several humanized murine **antibodies** specific for the antigen Lewis Y, which is recognized by the murine **antibody** Lewis Y. The **Lewis Y antigen** is expressed in normal tissues but the level of expression is higher in certain tumor types so that the antigen can be used as a marker for cells of some breast, colon, gastric, esophageal, pancreatic, duodenal, lung, bladder and renal carcinomas and gastric and islet cell neuroendocrine tumors. The invention also provides for numerous polynucleotide encoding humanized Lewis Y specific **antibodies**, expression vectors for producing humanized Lewis Y specific **antibodies**, and host cells for the recombinant production of the humanized **antibodies**. The invention also provides methods for detecting cancerous cells (in vitro and in vivo) using humanized Lewis Y specific **antibodies**. Additionally, the invention provides methods of treating cancer using humanized Lewis Y specific **antibodies**.

L9 ANSWER 19 OF 53 MEDLINE
AN 1999178673 MEDLINE
DN 99178673
TI Randomized phase II study of BR96-doxorubicin conjugate in patients with metastatic breast cancer.
AU Tolcher A W; Sugarman S; Gelmon K A; Cohen R; Saleh M; Isaacs C; Young L; Healey D; Onetto N; Slichenmyer W
CS British Columbia Cancer Agency, Vancouver, Canada.
SO JOURNAL OF CLINICAL ONCOLOGY, (1999 Feb) 17 (2) 478-84.
Journal code: JCO. ISSN: 0732-183X.
CY United States
DT (CLINICAL TRIAL)
(CLINICAL TRIAL, PHASE II)
Journal; Article; (JOURNAL ARTICLE)
(RANDOMIZED CONTROLLED TRIAL)
LA English
FS Priority Journals; Cancer Journals
EM 199906
EW 19990601
AB PURPOSE: BMS-182248-1 (BR96-doxorubicin immunoconjugate) is a chimeric human/mouse monoclonal **antibody** linked to approximately eight doxorubicin molecules. The **antibody** is directed against the **Lewis-Y antigen**, which is expressed on 75% of all breast cancers but is limited in expression on normal tissues. Preclinical xenograft models demonstrated significant antitumor activity, including cures. A randomized phase II design was chosen to estimate the activity of the BR96-doxorubicin conjugate in metastatic breast cancer in a study population with confirmed sensitivity to single-agent doxorubicin.
PATIENTS AND METHODS: Patients with measurable metastatic breast cancer and immunohistochemical evidence of Lewis-Y expression on their tumor received either BR96-doxorubicin conjugate 700 mg/m2 IV over 24 hours or doxorubicin 60 mg/m2 every 3 weeks. Patients were stratified on the basis of prior doxorubicin exposure, visceral disease, and institution. Cross-over to the opposite treatment arm was allowed with progressive or persistently stable disease. RESULTS: Twenty-three patients who had received a median of one prior chemotherapy regimen were assessable. There was one partial response (7%) in 14 patients receiving the BR96-doxorubicin conjugate and one complete response and three partial responses (44%) in nine assessable patients receiving doxorubicin. No patient experienced a clinically significant hypersensitivity reaction.

The toxicities were significantly different between the two treatment groups, with the BR96-doxorubicin conjugate group having limited hematologic toxicity, whereas gastrointestinal toxicities, including marked serum amylase and lipase elevations, nausea, and vomiting with gastritis, were prominent. CONCLUSION: The BR96-doxorubicin immunoconjugate has limited clinical antitumor activity in metastatic breast cancer. The gastrointestinal toxicities likely represent binding of the agent to normal tissues expressing the target antigen and may have compromised the delivery of the immunoconjugate to the tumor sites.

L9 ANSWER 20 OF 53 BIOSIS COPYRIGHT 2001 BIOSIS
AN 1999:208191 BIOSIS
DN PREV199900208191
TI Towards the development of peptide mimotopes of carbohydrate antigens as cancer vaccines.
AU Qiu, Jianping; Luo, Ping; Wasmund, Kelly; Steplewski, Zenon; Kieber-Emmons, Thomas (1)
CS (1) Department of Pathology and Laboratory Medicine, University of Pennsylvania, 36th and Hamilton Walk, Room 280, John Morgan Building, Philadelphia, PA, 19104-6082 USA
SO Hybridoma, (Feb., 1999) Vol. 18, No. 1, pp. 103-112.
ISSN: 0272-457X.
DT Article
LA English
SL English
AB Tumor-associated carbohydrate antigens are considered important targets in efforts to develop cancer vaccines. To further enhance vaccine efforts, we are developing peptide mimotopes of tumor-associated carbohydrate antigens that can elicit functional immune responses. Mapping peptide epitopes with anticarbohydrate **antibodies** can lend to defining structural relationships that can go undetected by screening of carbohydrate antigens alone. Here we contrast reactivity patterns for peptides using monoclonal **antibodies** (MAbs) directed to the neolactoseries related Lewis Y (LeY) and sialyl-Lewis X (sLeX) antigen and the GD3/GD2 ganglioside antigen. We observe that representative MAbs cross-react with a WRY-containing peptide and that this motif type is isolated by the respective monoclonal in peptide phage display screening. Primary immunization with multiple antigen peptide preparations with QS-21 adjuvant efficiently elicited cytotoxic IgM **antibodies** for a murine Meth A fibrosarcoma line expressing sLeX. The cytotoxicity of IgG polyclonal response was found to be as effective as IgM in mediating complement-dependent cytotoxicity against the Meth A line. These experiments suggest that peptide mimotopes of the LeY and sLeX tumor-associated carbohydrate antigen and QS-21 adjuvant could be considered as an immunogenic **therapeutic** vaccine in carcinoma and melanoma patients in the minimal residual disease setting.

L9 ANSWER 21 OF 53 USPATFULL
AN 1998:128389 USPATFULL
TI Branched hydrazone linkers
IN King, Dalton, 114 Wakefield St., Hamden, CT, United States 06517
Firestone, Raymond A., 900 Ridgeberry Rd., Ridgefield, CT, United States
06877
Trail, Pamela, 1419 Silo Rd., Yardley, PA, United States 19067
PI US 5824805 19981020
AI US 1996-770614 19961219 (8)
PRAI US 1995-9100 19951222 (60)

DT Utility
EXNAM Primary Examiner: Ceperley, Mary E.
LREP Savitsky, Thomas R.; Sorrentino, Joseph M.
CLMN Number of Claims: 13
ECL Exemplary Claim: 1
DRWN 2 Drawing Figure(s); 1 Drawing Page(s)
LN.CNT 2740
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Branched hydrazone linkers for linking a targeting ligand such as an **antibody** to a therapeutically active drug. The point of branching is at a polyvalent atom and the number of drugs increases by a factor of two for each generation of branching. A preferred drug is doxorubicin.

L9 ANSWER 22 OF 53 USPATFULL
AN 1998:4744 USPATFULL
TI Thioether conjugates
IN Willner, David, Hamden, CT, United States
Trail, Pamela A., Farmington, CT, United States
King, H. Dalton, Hamden, CT, United States
Hofstead, Sandra J., Middletown, CT, United States
Greenfield, Robert S., Wallingford, CT, United States
Braslawsky, Gary R., Glastonbury, CT, United States
PA Bristol-Myers Squibb Company, Princeton, NJ, United States (U.S. corporation)
PI US 5708146 19980113
AI US 1995-469840 19950606 (8)
RLI Division of Ser. No. US 1992-824951, filed on 23 Jan 1992, now patented, Pat. No. US 5622929
DT Utility
EXNAM Primary Examiner: Peselev, Elli
LREP Poor, Brian; Sorrentino, Joseph M.; Savitsky, Thomas R.
CLMN Number of Claims: 13
ECL Exemplary Claim: 1
DRWN 18 Drawing Figure(s); 17 Drawing Page(s)
LN.CNT 2044
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Provided are drug/ligand compounds of Formula (I): ##STR1## (I) in which

D is a drug moiety;

n is an integer from 1 to 10;

p is an integer from 1 to 6;

Y is O or NH.sub.2.sup.+ Cl.sup.- ;

z is 0 or 1;

q is about 1 to about 10;

X is a ligand; and,

A is a Michael Addition Adduct.

In a preferred embodiment, the ligand is an immunoglobulin, preferably a chimeric **antibody** or fragment thereof. Also provided are formulations comprising as an active ingredient a compound of Formula (I), intermediates useful for preparing the compounds of Formula (I), processes for preparing the compounds of Formula (I), and methods for

using the compounds of the invention.

L9 ANSWER 23 OF 53 USPATFULL
AN 1998:153859 USPATFULL
TI Methods for reducing tumor cell growth by using **antibodies** with broad tumor reactivity and limited normal tissue reactivity
IN Pastan, Ira, Potomac, MD, United States
Willingham, Mark C., Summerville, SC, United States
PA The United States of America as represented by the Department of Health and Human Services, Washington, DC, United States (U.S. government)
PI US 5846535 19981208
AI US 1995-467959 19950606 (8)
RLI Continuation-in-part of Ser. No. US 1994-363203, filed on 22 Dec 1994, now patented, Pat. No. US 5612032, issued on 18 Mar 1997 which is a division of Ser. No. US 1993-51133, filed on 22 Apr 1993, now abandoned which is a division of Ser. No. US 1990-596289, filed on 12 Oct 1990, now patented, Pat. No. US 5242813
DT Utility
EXNAM Primary Examiner: Eisenschenk, Frank C.
LREP Townsend and Townsend and Crew LLP
CLMN Number of Claims: 10
ECL Exemplary Claim: 1
DRWN 1 Drawing Figure(s); 1 Drawing Page(s)
LN.CNT 610
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The subject invention relates to methods for reducing tumor cell growth in a mammal by administering compositions which include an **antibody** having the binding specificity of a monoclonal **antibody** selected from the group comprising one of those referred to as B1, B3 or B5 conjugated to a toxin, radionuclide or drug.

L9 ANSWER 24 OF 53 USPATFULL
AN 1998:143653 USPATFULL
TI Multivalent and multispecific binding proteins, their manufacture and use
IN Holliger, Kaspar-Philipp, Cambridge, United Kingdom
Griffiths, Andrew David, Cambridge, United Kingdom
Hoogenboom, Hendricus Renerus Jacobus Matheus, Hasselt, Belgium
Malmqvist, Magnus, Upsala, Sweden
Marks, James David, Kensington, CA, United States
McGuinness, Brian Timothy, Cambridge, United Kingdom
Pope, Anthony Richard, Cambridge, United Kingdom
Prospero, Terence Derek, Cambridge, United Kingdom
Winter, Gregory Paul, Cambridge, United Kingdom
PA Medical Research Council, London, England (non-U.S. corporation)
Cambridge Antibody Technology Limited, Melbourn, England (non-U.S. corporation)
PI US 5837242 19981117
WO 9413804 19940623
AI US 1996-448418 19960514 (8)
WO 1993-GB2492 19931203
19960514 PCT 371 date
19960514 PCT 102(e) date
PRAI GB 1992-25453 19921204
GB 1993-816 19930116
EP 1993-303614 19930510
GB 1993-19969 19930922
DT Utility
EXNAM Primary Examiner: Walsh, Stephen; Assistant Examiner: Brown, Karen E.
LREP Marshall, O'Toole, Gerstein, Murray & Borun
CLMN Number of Claims: 85
ECL Exemplary Claim: 1
DRWN 52 Drawing Figure(s); 28 Drawing Page(s)

LN.CNT 5566
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Polypeptides comprising a first domain, which comprises a binding region of an immunoglobulin heavy chain variable region, and a second domain, which comprises a binding region of an immunoglobulin light chain variable region, the domains being linked but incapable of associating with each other to form an antigen binding site, associate to form antigen binding multimers, such as dimers, which may be multivalent or have multispecificity. The domains may be linked by a short peptide linker or may be joined directly together. Bispecific dimers may have longer linkers. Methods of preparation of the polypeptides and multimers and diverse repertoires thereof, and their display on the surface of bacteriophage for easy selection of binders of interest, are disclosed, along with many utilities.

L9 ANSWER 25 OF 53 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
AN 1998373132 EMBASE
TI Drug targeting systems for cancer chemotherapy.
AU Sachdeva M.S.
CS M.S. Sachdeva, College of Pharmacy, Florida A and M University, Tallahassee, FL 32307, United States
SO Expert Opinion on Investigational Drugs, (1998) 7/11 (1849-1864).
Refs: 224
ISSN: 1354-3784 CODEN: EOIDER
CY United Kingdom
DT Journal; General Review
FS 016 Cancer
030 Pharmacology
037 Drug Literature Index
039 Pharmacy
LA English
SL English
AB Tumour specific drug targeting has been a very actively investigated area for over 2 decades. Various approaches have involved the use of drug delivery systems that can localise the anticancer agent at the tumour site without damaging the normal cells. For this purpose, various delivery systems that have been utilised are liposomes, microspheres and recently, nanoparticles. Two liposome formulations containing anticancer drugs for example, adriamycin and daunomycin are already on the market in the USA and Europe. Microspheres are also being investigated for delivering various anticancer drugs and protein/peptides for anticancer treatment, and several formulations are in Phase I/II clinical trials. Antitumour drugs have also been linked to tumour specific monoclonal **antibodies** via various chemical linkages. Doxorubicin was linked to a chimeric monoclonal **antibody** that was targeted to the **Lewis Y antigen**. Though this conjugate initially showed potential, it was recently dropped from Phase II clinical trials. Another approach with monoclonal **antibodies** has been the use of immunotoxins. Immunotoxins initially showed promise as potential anticancer agents at picomolar concentrations but several clinical and preclinical studies have not shown much promise in this regard. Drug containing liposomes and microspheres have been further linked to tumour specific monoclonal **antibodies** to enhance their tumour specificity. Most of the studies with immunoliposomes or targeted microspheres have not gone beyond the preclinical studies. New **therapeutic** approaches are presently emerging based on natural products like cytokines, peptide growth factor antagonists, antisense oligonucleotides and specific genes. These approaches need the help of delivery systems to deliver these complex molecules to tumour cells. One of the current pursued approaches is the use of cationic liposomes.

Several clinical studies are undergoing with various cationic liposomes and the next few years will demonstrate the usefulness of this approach. In recent years, the problems in cancer treatment have been complicated with the emergence of resistance strains leading to resistant and cross-resistant tumour cells. Several agents have been used to overcome

or

reverse drug-resistance in solid tumours and it remains a highly pursued area in cancer treatment.

L9 ANSWER 26 OF 53 MEDLINE
AN 1999113220 MEDLINE
DN 99113220
TI Targeted gene transfer for adenocarcinoma using a combination of tumor-specific **antibody** and tissue-specific promoter.
AU Kurane S; Krauss J C; Watari E; Kannagi R; Chang A E; Kudoh S
CS Fourth Department of Internal Medicine, Nippon Medical School, Tokyo.
SO JAPANESE JOURNAL OF CANCER RESEARCH, (1998 Nov) 89 (11) 1212-9.
Journal code: HBA. ISSN: 0910-5050.
CY Japan
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 199904
EW 19990402
AB We have developed a highly specific gene transfer method for adenocarcinoma using a monoclonal **antibody** against tumor-specific antigen coupled with a plasmid containing the carcinoembryonic antigen (CEA)-specific promoter. The chimeric CEA promoter (CC promoter), which contained an enhancer from the immediate early gene of cytomegalovirus and the CEA promoter, achieved 4- to 5-fold higher transgene expression in CEA-producing cells than the original CEA promoter while maintaining CEA specificity. Furthermore, a complex of a monoclonal **antibody** against **Lewis Y antigen** (LYA), the CC promoter-containing plasmid and cationic liposomes (DOTAP) achieved specific gene expression in CEA-producing and LYA-positive adenocarcinoma cell lines that was 200-fold more efficient than in CEA-non-producing and LYA-negative cell lines during a short in vitro incubation. This strategy may be applicable for clinical gene therapy.

L9 ANSWER 27 OF 53 MEDLINE
AN 1999034515 MEDLINE
DN 99034515
TI Comparison of recombinant immunotoxins against LeY antigen expressing tumor cells: influence of affinity, size, and stability.
AU Bera T K; Pastan I
CS Laboratory of Molecular Biology, DBS, National Cancer Institute, National Institutes of Health, Building 37, Room 4E16, 37 Convent Drive MSC 4255, Bethesda, Maryland 20892-4255, USA.
SO BIOCONJUGATE CHEMISTRY, (1998 Nov-Dec) 9 (6) 736-43.
Journal code: A1T. ISSN: 1043-1802.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199903
EW 19990304
AB Monoclonal **antibody** B3 (MAb B3) reacts with many epithelial cancers. It recognizes a carbohydrate antigen (Ley) which is expressed in a variety of solid tumors including breast and colon. We have used the

Fab

portion of MAb B3 and a portion of the constant domain of human IgG1 to make recombinant immunotoxins of different compositions. The toxin component employed is a truncated form of Pseudomonas exotoxin (PE38).

The

light chain or Fd of the **antibody** was cloned from hybridoma RNA and fused to PE38. Immunotoxin (IT) was then expressed in Escherichia coli as a fusion protein and refolded with either the Fd or the light chain. We have also made B3(Fab) immunotoxins of different sizes ranging 85-140 kDa, by introducing different portions of the constant domain of human IgG1 at the junction of Fd and PE38 fusion site. We compared the properties of the resulting immunotoxins with existing anti-Ley immunotoxins side by side. All recombinant Fab-immunotoxins made in this study were cytotoxic to antigen-positive cancer cell lines. However, in contrast to the B3(scFv) immunotoxin, the B3(Fab) immunotoxins are very stable, retaining 90% of their activity after 24 h of incubation in human serum albumin at 37 degreesC. A pharmacokinetics study with these immunotoxin molecules showed a longer survival in the circulation of mice compared to the smaller Fv immunotoxins. The smaller size of the Fab immunotoxins compared to B3Lys-PE38 and the increased T1/2 value compared to B3(scFv)-PE38 and B3(dsFv)-PE38 make these recombinant immunotoxins alternative **therapeutic** agents to treat Ley antigen positive cancers.

L9 ANSWER 28 OF 53 MEDLINE
AN 1998256190 MEDLINE
DN 98256190
TI Expression of Lex antigen in Schistosoma japonicum and S.haematobium and immune responses to Lex in infected animals: lack of Lex expression in other trematodes and nematodes.
AU Nyame A K; Debose-Boyd R; Long T D; Tsang V C; Cummings R D
CS Department of Biochemistry and Molecular Biology, University of Oklahoma Health Science Center, BRC 417, 975 N.E. 10th Street, Oklahoma City, OK 73104, USA.
NC AI26725 (NIAID)
AI052590 (NIAID)
SO GLYCOBIOLOGY, (1998 Jun) 8 (6) 615-24.
Journal code: BEL. ISSN: 0959-6658.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199809
EW 19980904
AB Adults of the human parasitic trematode Schistosoma mansoni, which causes hepatosplenic/intestinal complications in humans, synthesize glycoconjugates containing the Lewis x (Lex) Galbeta1-->4(Fucalpha1-->3)GlcNAcbeta1-->R, but not sialyl Lewis x (sLex), antigen. We now report on our analyses of Lexand sLexexpression in S.haematobium and S.japonicum, which are two other major species of human schistosomes that cause disease, and the possible autoimmunity to these antigens in infected individuals. Antigen expression was evaluated by both ELISA and Western blot analyses of detergent extracts of parasites using monoclonal **antibodies**. Several high molecular weight glycoproteins in both S. haematobium and S. japonicum contain the Lexantigen, but no sialyl Lexantigen was detected. In addition, sera from humans and rodents infected with S.haematobium and S.japonicum contain **antibodies** reactive with Lex. These results led us to investigate whether Lexantigens are expressed in other helminths, including the parasitic trematode Fasciola hepatica , the parasitic nematode Dirofilaria immitis (dog heartworm), the ruminant nematode Haemonchus contortus , and the free-living nematode Caenorhabditis elegans . Neither Lexnor sialyl-Lexis detectable in these other helminths. Furthermore, none of the helminths,

including schistosomes, express Lea, Leb, Ley, or the H-type 1 antigen. However, several glycoproteins from all helminths analyzed are bound by Lotus tetragonolobus agglutinin , which binds Fucalpha1-->3GlcNAc, and Wisteria floribunda agglutinin, which binds GalNAcbeta1-->4GlcNAc (lacdiNAc or LDN). Thus, schistosomes may be unique among helminths in expressing the Lexantigen, whereas many different helminths may express alpha1,3-**fucosylated** glycans and the LDN motif.

L9 ANSWER 29 OF 53 MEDLINE
AN 1999114133 MEDLINE
DN 99114133
TI Transfer of chimeric receptor gene made of variable regions of tumor-specific **antibody** confers anticarbohydrate specificity on T cells.
AU Mezzanzanica D; Canevari S; Mazzoni A; Figini M; Colnaghi M I; Waks T; Schindler D G; Eshhar Z
CS Oncologia Sperimentale E, Istituto Nazionale Tumori, Milano, Italy.
SO CANCER GENE THERAPY, (1998 Nov-Dec) 5 (6) 401-7.
Journal code: CE3. ISSN: 0929-1903.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199905
EW 19990504
AB The antitumor specificity of T cells can be induced by gene transfer using a recently developed **therapeutic** approach (T body). In this work, we genetically conferred anticarbohydrate specificity onto T cells using the variable regions of monoclonal **antibody** MLuC1, which binds the Lewis(Y) (LeY) tumor-associated antigen that is overexpressed on several human carcinomas. The variable regions of MLuC1, which are in a single-chain Fv (ScFv) configuration, were cloned and spliced in a eukaryotic expression vector with both the gene encoding the signal-transducing gamma-chain of the human Fcgamma receptor and a flexible hinge domain. The chimeric ScFv-gamma gene was expressed in a murine cytotoxic T-cell hybridoma. Transfectants receiving vector only served as a negative control (mock). Screening for functional transfectants was carried out using a tumor growth inhibition assay. The soluble form of MLuC1 ScFv was recovered from bacteria periplasm and tested for binding to LeY-expressing cells by the fluorescence-activated cell sorter analysis. Despite the low binding ability of the soluble MLuC1 ScFv, 7 of 13 genetically engineered cytotoxic T lymphocyte clones inhibited the growth of LeY-positive cells and did not affect growth of LeY-negative cells. None of the mock clones tested specifically inhibited tumor growth. These data indicate that, by chimeric MLuC1 ScFv-gamma gene transfer, it is possible to confer anticarbohydrate specificity onto T cells and extend the applicability of the T-body approach to tumor-associated antigens that are naturally not recognized by T cells.

L9 ANSWER 30 OF 53 MEDLINE
AN 1998139348 MEDLINE
DN 98139348
TI Immunogenicity of synthetic conjugates of Lewis(y) oligosaccharide with proteins in mice: towards the design of anticancer vaccines.
AU Kudryashov V; Kim H M; Ragupathi G; Danishefsky S J; Livingston P O; Lloyd K O
CS Immunology Program, Memorial Sloan-Kettering Cancer Center, New York, NY 10021, USA.
NC CA 71506 (NCI)
CA 61422 (NCI)

AI 16943 (NIAID)
+
SO CANCER IMMUNOLOGY, IMMUNOTHERAPY, (1998 Feb) 45 (6) 281-6.
Journal code: CN3. ISSN: 0340-7004.
CY GERMANY: Germany, Federal Republic of
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 199805
EW 19980501
AB Many human carcinomas overexpress the Lewis(y) (Le[y]) blood-group epitope
[Fucalpha1-->2Galbeta1-->4 (Fucalpha1-->3)GlcNAcbeta1-->3Gal-]. With a view to developing Le(y) based vaccines we have examined the immunogenicity of Le(y)-protein conjugates in mice. Le(y) pentasaccharide was synthesized as its allyl glycoside and coupled to keyhole limpet hemocyanin (KLH) by reductive amination or by a novel method utilizing a maleido-derivitized alkyl carboxyhydrazide as a bridging group to 2-iminothiolane-derivitized KLH. Le(y) oligosaccharide was also coupled to
bovine serum albumin by reductive amination. Immunization of groups of mice with the three conjugates, together with the immunological adjuvant QS21, showed that Le(y) oligosaccharide directly coupled to KLH was the most efficient conjugate for eliciting IgG and IgM **antibody** responses to naturally occurring forms of Le(y) epitopes carried on mucins
and glycolipids. These **antibodies** were also reactive with and cytotoxic to a human breast cancer cell line expressing Le(y) (MCF-7). These experiments suggest that Le(y)-KLH antigen and QS21 adjuvant could be considered as an immunogenic **therapeutic** vaccine in carcinoma patients.

L9 ANSWER 31 OF 53 USPATFULL
AN 97:33724 USPATFULL
TI Thioether conjugates
IN Willner, David, Hamden, CT, United States
Trail, Pamela A., Farmington, CT, United States
King, H. Dalton, Hamden, CT, United States
Hofstead, Sandra J., Middletown, CT, United States
Greenfield, Robert S., Wallingford, CT, United States
Braslawsky, Gary R., Glastonbury, CT, United States
PA Bristol-Myers Squibb Company, New York, NY, United States (U.S. corporation)
PI US 5622929 19970422
AI US 1992-824951 19920123 (7)
DT Utility
EXNAM Primary Examiner: Peselev, Elli
LREP Bristol-Myers Squibb Co.
CLMN Number of Claims: 52
ECL Exemplary Claim: 6
DRWN 18 Drawing Figure(s); 17 Drawing Page(s)
LN.CNT 2212
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Provided are drug/ligand compounds of Formula (I): ##STR1## in which D is a drug moiety;

n is an integer from 1 to 10;

p is an integer from 1 to 6;

Y is O or NH.sub.2.sup.+ Cl.sup.- ;

z is 0 or 1;

q is about 1 to about 10;

X is a ligand; and,

A is a Michael Addition Adduct.

In a preferred embodiment, the ligand is an immunoglobulin, preferably a chimeric **antibody** or fragment thereof. Also provided are formulations comprising as an active ingredient a compound of Formula (I), intermediates useful for preparing the compounds of Formula (I), processes for preparing the compounds of Formula (I), and methods for using the compounds of the invention.

L9 ANSWER 32 OF 53 USPATFULL
AN 97:16169 USPATFULL
TI Thioether conjugates
IN Willner, David, Hamden, CT, United States
Trail, Pamela A., Farmington, CT, United States
King, H. Dalton, Hamden, CT, United States
Hofstead, Sandra J., Middletown, CT, United States
Greenfield, Robert S., Wallingford, CT, United States
Braslawsky, Gary R., Glastonbury, CT, United States
PA Bristol-Myers Squibb Company, New York, NY, United States (U.S. corporation)
PI US 5606017 19970225
AI US 1995-468162 19950606 (8)
RLI Division of Ser. No. US 1992-824951, filed on 23 Jan 1992
DT Utility
EXNAM Primary Examiner: Peselev, Elli
CLMN Number of Claims: 20
ECL Exemplary Claim: 1
DRWN 18 Drawing Figure(s); 17 Drawing Page(s)
LN.CNT 2095
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Provided are drug/ligand compounds of Formula (I): ##STR1## in which D is a drug moiety;

n is an integer from 1 to 10;

p is an integer from 1 to 6;

Y is O or NH.sub.2.sup.+ Cl.sup.- ;

z is 0 or 1;

q is about 1 to about 10;

X is a ligand; and,

A is a Michael Addition Adduct.

In a preferred embodiment, the ligand is an immunoglobulin, preferably a chimeric **antibody** or fragment thereof. Also provided are formulations comprising as an active ingredient a compound of Formula (I), intermediates useful for preparing the compounds of Formula (I), processes for preparing the compounds of Formula (I), and methods for using the compounds of the invention.

L9 ANSWER 33 OF 53 USPATFULL
AN 97:7681 USPATFULL
TI Bryodin 2 a ribosome-inactivating protein isolated from the plant Bryonia dioica

IN Siegall, Clay B., Edmonds, WA, United States
Gawlak, Susan L., Bellevue, WA, United States
Marquardt, Hans, Mercer Island, WA, United States
PA Bristol-Myers Squibb Company, New York, NY, United States (U.S. corporation)
PI US 5597569 19970128
AI US 1994-324301 19941020 (8)
RLI Continuation-in-part of Ser. No. US 1993-141891, filed on 25 Oct 1993, now abandoned
DT Utility
EXNAM Primary Examiner: Chan, Christina Y.; Assistant Examiner: Gambel, Phillip
CLMN Number of Claims: 41
ECL Exemplary Claim: 1
DRWN 16 Drawing Figure(s); 16 Drawing Page(s)
LN.CNT 1876
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The present invention discloses a new ribosome-inactivating protein, bryodin 2, isolated from the plant Bryonia dioica. This ribosome-inactivating protein (RIP) is a type IRIP having a single polypeptide chain and no cellular receptor domain. Like many type I RIPs, bryodin 2 has a molecular weight of about 27,000 daltons and a pI of 9.5. Bryodin 2 differs from previously identified ribosome-inactivating protein in its amino acid composition, amino acid sequence, and toxicity in vitro and in vivo. Bryodin 2 is useful, as are other type I ribosome-inactivating proteins, as an abortifacient, immunomodulator, anti-tumor or anti-viral agent. Compositions comprising bryodin 2 as an immunoconjugate or fusion molecule are particularly useful to kill cells of a target population.

L9 ANSWER 34 OF 53 USPATFULL
AN 97:22479 USPATFULL
TI Method for diagnosing tumors using mouse monoclonal **antibodies**
IN Pastan, Ira, Potomac, MD, United States
Willingham, Mark C., Bethesda, MD, United States
PA The United States of America as represented by the Department of Health and Human Services, Washington, DC, United States (U.S. government)
PI US 5612032 19970318
AI US 1994-363203 19941222 (8)
RLI Division of Ser. No. US 1993-51133, filed on 22 Apr 1993, now abandoned which is a division of Ser. No. US 1990-596289, filed on 12 Oct 1990, now patented, Pat. No. US 5242813
DT Utility
EXNAM Primary Examiner: Adams, Donald E.
LREP Townsend and Townsend and Crew LLP
CLMN Number of Claims: 3
ECL Exemplary Claim: 1
DRWN 1 Drawing Figure(s); 1 Drawing Page(s)
LN.CNT 597
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The subject invention relates to monoclonal **antibodies** and uses thereof. In particular, the invention relates to three monoclonal **antibodies**, referred to as B1, B3, and B5, which are useful in the treatment and diagnosis of many forms of cancer.

L9 ANSWER 35 OF 53 MEDLINE
AN 97435272 MEDLINE
DN 97435272
TI Expression of alpha-1,3-galactose and other type 2 oligosaccharide structures in a porcine endothelial cell line transfected with human alpha-1,2-fucosyltransferase cDNA.
AU Sepp A; Skacel P; Lindstedt R; Lechler R I

CS Department of Immunology, Royal Postgraduate Medical School, DuCane Road, London W12 0NN, United Kingdom.
SO JOURNAL OF BIOLOGICAL CHEMISTRY, (1997 Sep 12) 272 (37) 23104-10. Journal code: HIV. ISSN: 0021-9258.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 199712
EW 19971201
AB The binding of xenoreactive natural **antibodies** to the Galalpha1-3Galbeta1-4GlcNAc (alpha-galactose) oligosaccharide epitope on pig cells activates the recipient's complement system in pig to primate xenotransplantation. Expression of human alpha-1, 2-fucosyltransferase in pigs has been proposed as a strategy for reducing the expression level of the alpha-galactose epitope, thereby rendering the pig organs more suitable for transplantation into humans. The aim of this study was to examine how the cell surface expression of alpha-galactose, H, and related **fucosylated** and sialylated structures on a pig liver endothelial cell line is affected by transfection of human alpha-1,2-fucosyltransferase cDNA. Nontransfected and mock-transfected cells expressed alpha-galactose, alpha-2,3-sialylated, and alpha-2,6-sialylated epitopes strongly, with low level expression of type 2 H and LewisX. By contrast, expression of the H epitope was increased 5-8-fold in transfected cells with a 40% reduction in the expression of alpha-galactose epitope and a 50% decrease in sialylation, as measured by binding of Maackia amurensis and Sambuccus nigra agglutinins. LewisX expression was reduced to background levels, while the LewisY neoepitope was induced in human alpha-1,2-fucosyltransferase-expressing pig cells. The activities of endogenous alpha-1,3-galactosyltransferase, alpha-1,3-fucosyltransferases, and alpha-2,3- and alpha-2, 6-sialyltransferases acting on lactosamine were unaffected. Our results show that a reduction in alpha-galactose epitope expression in porcine endothelial cells transfected with human alpha-1, 2-fucosyltransferase cDNA may be achieved but at the expense of considerable distortion of the overall cell surface glycosylation profile, including the appearance of carbohydrate epitopes that are absent from the parent cells.

L9 ANSWER 36 OF 53 MEDLINE
AN 1998021974 MEDLINE
DN 98021974
TI Antitumor activity of carcinoma-reactive BR96-doxorubicin conjugate against human carcinomas in athymic mice and rats and syngeneic rat carcinomas in immunocompetent rats.
AU Sjogren H O; Isaksson M; Willner D; Hellstrom I; Hellstrom K E; Trail P A
CS Department of Cell and Molecular Biology, University of Lund, Sweden.
SO CANCER RESEARCH, (1997 Oct 15) 57 (20) 4530-6. Journal code: CNF. ISSN: 0008-5472.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 199801
EW 19980104
AB The internalizing monoclonal **antibody** BR96 was conjugated to the anticancer drug doxorubicin (DOX) using an acid-labile hydrazone bond to DOX and a thioether bond to the monoclonal **antibody**. The resulting conjugate, termed BR96-DOX, binds to a tumor-associated **Lewis(y) antigen** that is abundantly expressed on the surface of human carcinoma cells. BR96-DOX binds to RCA, a human colon carcinoma cell line, and BN7005, a transplantable colon carcinoma induced in a Brown Norway (BN) rat by 1,2-dimethyl-hydrazine. BR96-DOX produces cures of established s.c. RCA human colon carcinomas in athymic

mice and rats. BR96-DOX also cured both s.c. and intrahepatic BN7005 tumors in immunocompetent BN rats. Unconjugated DOX, given at its maximum tolerated dose, and matching doses of nonbinding IgG-DOX conjugate were not active against RCA or BN7005 carcinomas. An anticonjugate **antibody** response was produced in BN rats treated with BR96-DOX. However, this could be largely prevented by administering the immunosuppressive drug deoxyspergualin. These results confirm the concept of **antibody**-directed therapy in models in which the targeted antigen is expressed both in normal tissues and tumors. The findings in BN7005 further demonstrate efficacy of BR96-DOX therapy in a model in which the tumor is syngeneic and the host is immunocompetent.

L9 ANSWER 37 OF 53 MEDLINE
AN 97396503 MEDLINE
DN 97396503
TI Detection of rare human breast cancer cells. Comparison of an immunomagnetic separation method with immunocytochemistry and RT-PCR.
AU Berois N; Varangot M; Osinaga E; Babino A; Caignault L; Muse I; Roseto A
CS Depto. de Bioquimica, Facultad de Medicina, Montevideo, Uruguay.
SO ANTICANCER RESEARCH, (1997 Jul-Aug) 17 (4A) 2639-46.
Journal code: 59L. ISSN: 0250-7005.
CY Greece
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 199711
EW 19971101
AB BACKGROUND: The detection of occult carcinoma cells in patients with breast cancer may aid determination of prognosis and the development of new **therapeutic** approaches. In this study, we report a new method to detect rare human breast cancer cells, which combines an immunomagnetic separation (IMS) procedure with cytokeratin 19 (CK 19) immunostaining. MATERIALS AND METHODS: Four monoclonal **antibodies** (MAb) previously characterized against cell surface antigens (1BE12, ED8, 7B10 and 83D4), were evaluated for IMS optimization. Immunoseparated epithelial cells were identified using a MAb against CK 19. We compared the IMS procedure with the immunocytochemistry (ICC) and the RT-PCR for CK
19 on an "in vitro" experimental model. RESULTS: The best results in IMS procedures were obtained using MAbs 1BE12 (directed against **Lewis y antigen**) and ED8 (directed against MUC 1). In reconstitution experiments, using several ratios of T47D cells mixed with peripheral-blood mononuclear (PBMN) cells, the IMS procedure reliably detects one mammary carcinoma cell in 5 x 10(5) PBMN cells, whereas the ICC detects up to one T47D cell per 10(5) PBMN cells. The best sensitivity
was observed with the RT-PCR (up to one T47D cell per 10(6) PBMN cells). We found the same high specificity with the three methods evaluated. CONCLUSIONS: The IMS procedure using MAbs 1BE12 or ED8 associated with CK 19 immunostaining is a specific, sensitive, and feasible method for the detection of rare human breast cancer cells. This method proved to be better than the ICC staining but its sensitivity was lower than that of RT-PCR for CK 19.

L9 ANSWER 38 OF 53 USPATFULL
AN 96:67931 USPATFULL
TI Cloning and expression of a gene encoding bryodin 1 from Bryonia dioica
IN Siegall, Clay B., Edmonds, WA, United States
PA Bristol-Myers Squibb, New York, NY, United States (U.S. corporation)
PI US 5541110 19960730
AI US 1994-245754 19940517 (8)
DT Utility
EXNAM Primary Examiner: Wax, Robert A.; Assistant Examiner: Lau, Kawai
CLMN Number of Claims: 11

ECL Exemplary Claim: 1
DRWN 13 Drawing Figure(s); 9 Drawing Page(s)
LN.CNT 1075
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The molecular cloning and expression of biologically active ribosome-inactivating protein bryodin 1 are described. A complete amino acid and oligonucleotide sequence encoding bryodin 1 are also described.

Further, plasmids, expression vectors comprising a nucleotide sequence encoding bryodin 1 and transformed host cells are described. Isolation and characterization of the nucleotide sequence for bryodin 1 enables the recombinant production of large amount of bryodin 1 for use in vitro

or in vivo directly or as ligand/toxin conjugates or fusion proteins. These compositions can be used to selectively kill undesired cells such as cancer cells, infected cells, bacteria.

L9 ANSWER 39 OF 53 USPATFULL
AN 96:12810 USPATFULL
TI Monoclonal **antibody** BR 96 and chimeric monoclonal **antibodies** having the variable region of MAB BR96, which bind to a variant of ley antigen on human carcimona cells
IN Hellstrom, Ingegerd, Seattle, WA, United States
Hellstrom, Karl E., Seattle, WA, United States
Bruce, Kim F., Seattle, WA, United States
Schreiber, George J., Redmond, WA, United States
PA Oncogen Limited Partnership, United States
PI US 5491088 19960213
AI US 1993-57444 19930505 (8)
RLI Continuation of Ser. No. US 1990-544246, filed on 26 Jun 1990, now abandoned which is a continuation-in-part of Ser. No. US 1989-374947, filed on 30 Jun 1989, now abandoned
DT Utility
EXNAM Primary Examiner: Hutzell, Paula K.
LREP Merchant, Gould, Smith, Edell, Welter, & Schmidt
CLMN Number of Claims: 12
ECL Exemplary Claim: 1
DRWN 27 Drawing Figure(s); 27 Drawing Page(s)
LN.CNT 2238
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The present invention relates to novel **antibodies** reactive with human carcinoma cells. More particularly, the **antibodies** of the invention include: a murine monoclonal **antibody**, BR96; a human/murine chimeric **antibody**, ChiBR96; and a F(ab').sub.2 fragment of BR96. These **antibodies** are reactive with a cell membrane antigen on the surface of human carcinomas. The **antibodies** display a high degree of selectivity for carcinoma cells and possess the ability to mediate ADCC and CDC activity. In addition, the **antibodies** of the invention internalize within the carcinoma cells to which they bind. The **antibodies** also have a unique feature in that they are cytotoxic when used in the unmodified form, at specified concentrations.

L9 ANSWER 40 OF 53 USPATFULL
AN 96:101284 USPATFULL
TI Pharmaceutical composition against AIDS
IN Honda, Mitsuo, Tokyo, Japan
Yamazaki, Shudo, Tokyo, Japan
Horie, Ryuichi, Kawasaki, Japan
Saito, Takashi, Ayase, Japan
Shigeta, Katsuyoshi, Yokohama, Japan
Ota, Noriyuki, Sagamihara, Japan
PA Tosoh Corporation, Shinnanyo, Japan (non-U.S. corporation)
PI US 5571512 19961105

AI US 1993-102218 19930805 (8)
PRAI JP 1992-237594 19920814
DT Utility
EXNAM Primary Examiner: Feisee, Lila
LREP Foley & Lardner
CLMN Number of Claims: 1
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 380
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB A pharmaceutical composition against AIDS, which contains, as an active ingredient, an **antibody** capable of recognizing glycolipid derived from Echinoidea.

L9 ANSWER 41 OF 53 USPATFULL
AN 96:91824 USPATFULL
TI Humanized **antibodies** that recognize difucosyl Lewis blood group antigens Y-6 and B-7-2
IN Co, Man S., Cupertino, CA, United States
Loibner, Hans, Vienna, Austria
PA Sandoz Ltd., Basel, Switzerland (non-U.S. corporation)
PI US 5562903 19961008
AI US 1993-53171 19930422 (8)
RLI Continuation of Ser. No. US 1992-932180, filed on 19 Aug 1992, now abandoned
PRAI GB 1991-18013 19910821
GB 1992-4514 19920302
DT Utility
EXNAM Primary Examiner: Hutzell, Paula K.
LREP Townsend and Townsend and Crew LLP
CLMN Number of Claims: 12
ECL Exemplary Claim: 1
DRWN 45 Drawing Figure(s); 42 Drawing Page(s)
LN.CNT 1705
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Humanized monoclonal **antibodies** that recognize the difucosyl Lewis blood group antigens Y-6 and B-7-2 are disclosed. The **antibodies** have a humanized light chain variable region and a humanized heavy chain variable region with CDRs from **antibody** BR55-2. Fragments of the **antibodies** and pharmaceutical compositions containing them are also disclosed.

L9 ANSWER 42 OF 53 USPATFULL
AN 96:48176 USPATFULL
TI Monoclonal **antibody** in destruction of small cell lung carcinoma
IN Loibner, Hans, Vienna, Austria
Scholz, Dieter, Vienna, Austria
PA Sandoz Ltd., Basel, Switzerland (non-U.S. corporation)
PI US 5523085 19960604
AI US 1995-378890 19950124 (8)
RLI Continuation of Ser. No. US 1993-93416, filed on 19 Jul 1993, now abandoned which is a continuation of Ser. No. US 1991-661745, filed on 27 Feb 1991, now abandoned
PRAI DE 1990-4006308 19900228
DT Utility
EXNAM Primary Examiner: Feisee, Lila; Assistant Examiner: Loring, Susan A.
LREP Townsend and Townsend and Crew
CLMN Number of Claims: 10
ECL Exemplary Claim: 1
DRWN 10 Drawing Figure(s); 6 Drawing Page(s)
LN.CNT 532
AB Monoclonal **antibody** BR55-2 and fragments thereof having the specificity of monoclonal **antibody** BR55-2, and variants

thereof, are useful in the treatment of small cell lung carcinoma.

L9 ANSWER 43 OF 53 MEDLINE
AN 1999035177 MEDLINE
DN 99035177
TI Cytotoxic and antitumor activity of a recombinant tumor necrosis factor-B1(Fv) fusion protein on LeY antigen-expressing human cancer cells.
AU Scherf U; Benhar I; Webber K O; Pastan I; Brinkmann U
CS Laboratory of Molecular Biology, Division of Basic Sciences, National Cancer Institute, NIH, Bethesda, Maryland 20892-4255, USA.
SO CLINICAL CANCER RESEARCH, (1996 Sep) 2 (9) 1523-31.
Journal code: C2H. ISSN: 1078-0432.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199904
EW 19990404
AB We have constructed a fusion protein composed of tumor necrosis factor alpha (TNF-alpha) fused at its COOH terminus to the scFv region of monoclonal **antibody** (mAb) B1, an **antibody** that recognizes LeY antigen present on many human cancer cells. Our rationale for fusing the scFv to the COOH terminus of TNF was to diminish the binding of the fusion protein to TNF receptors because the COOH terminus of TNF is involved in binding, and thus to partially inactivate (detoxify) the molecule. The Fv region should then target and accumulate the fusion protein on cancer cells, which should compensate for the reduced binding affinity of the TNF moiety and lead to selective killing of TNF-sensitive antigen-expressing cancer cells. The fusion protein was expressed in Escherichia coli and found in insoluble inclusion bodies. After refolding and purification by anion exchange, Ni-NTA affinity, and size-exclusion chromatography, we obtained monomeric TNF-B1(Fv). This molecule binds to LeY antigen on cancer cells with the same affinity as B1(scFv) and B1(scFv) immunotoxins but with significantly lower affinity to the TNF receptor compared to the TNF trimer. TNF-B1(Fv) is very toxic to LeY antigen-expressing cancer cells that are sensitive to TNF (e.g., MCF-7 breast or CRL-1739 gastric cancer cells). This cytotoxicity is **antibody** targeted and TNF mediated because it can be prevented (as shown on MCF-7 cells) by an **antibody** competing for LeY antigen binding and by an **antibody** that neutralizes TNF-alpha. TNF-B1(Fv) kills TNF-alpha-sensitive cells that do not express the target antigen only at much higher doses than TNF trimer, and it does not kill LeY-bearing but TNF-alpha-resistant cells. TNF-B1(Fv) can cause significant tumor regression of MCF-7 tumor xenografts in mice at doses that are not toxic to the mice. Thus, the reduced binding of the TNF moiety to TNF receptors, combined with binding of the B1(Fv) portion to LeY antigen, makes TNF-B1(Fv) an agent for selective killing of LeY-expressing TNF-sensitive cancer cells.

L9 ANSWER 44 OF 53 MEDLINE
AN 96387569 MEDLINE
DN 96387569
TI Molecular recognition of the **Lewis Y antigen** by monoclonal **antibodies**.
AU Blaszczyk-Thurin M; Murali R; Westerink M A; Steplewski Z; Co M S; Kieber-Emmons T
CS Wistar Institute of Anatomy and Biology, University of Pennsylvania, Philadelphia 19104-6082, USA.
SO PROTEIN ENGINEERING, (1996 May) 9 (5) 447-59.
Journal code: PR1. ISSN: 0269-2139.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)

LA English
FS Priority Journals
EM 199702
EW 19970204
AB The murine monoclonal **antibody** BR55-2 is directed against the tumor-associated antigen Lewis Y oligosaccharide. The Lewis Y core antigen is a difucosylated structure consisting of four hexose units. Analysis of binding profiles of lactoseries isomeric structures by BR55-2 suggest that the binding epitope includes the OH-4 and OH-3 groups of the beta-D-galactose unit, the 6-CH3 groups of the two fucose units and the N-acetyl group of the subterminal beta-D-N-acetylglucosamine (beta DGlcNAc). To elucidate the molecular recognition properties of BR55-2 for the Y antigen, BR55-2 was cloned, sequenced and its three-dimensional structure was examined by molecular modeling. The crystal structure of BR96, another anti-Lewis Y **antibody**, solved in complex with a nonoate methyl ester Lewis Y tetrasaccharide, and the lectin IV protein in complex with a Lewis b tetrasaccharide core were used as a guide to probe the molecular basis for BR55-2 antigen recognition and specificity. Our modeling study shows that BR55-2 shares similar recognition features for the difucosylated type 2 lactoseries Lewis Y structure observed in the BR96-sugar complex. We observe that a major source of specificity for the Lewis Y structure by anti-Y **antibodies** emanates from interaction with the beta-D-N-acetylglucosamine residue and the nature of the structures extended at the reducing site of the **fucosylated** lactosoamine.

L9 ANSWER 45 OF 53 MEDLINE
AN 96197741 MEDLINE
DN 96197741
TI Treatment of advanced solid tumors with immunotoxin LMB-1: an **antibody** linked to Pseudomonas exotoxin.
AU Pai L H; Wittes R; Setser A; Willingham M C; Pastan I
CS Laboratory of Molecular Biology, National Cancer Institute, National Institutes of Health, Bethesda, Maryland 20892, USA.
SO NATURE MEDICINE, (1996 Mar) 2 (3) 350-3.
Journal code: CG5. ISSN: 1078-8956.
CY United States
DT (CLINICAL TRIAL)
(CLINICAL TRIAL, PHASE I)
Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199608
AB Immunotoxin LMB-1 is composed of monoclonal **antibody** B3 chemically linked to PE38, a genetically engineered form of Pseudomonas exotoxin. B3 recognizes a carbohydrate antigen (Le(Y)) present on many human solid tumors. LMB-1 has excellent antitumor activity in nude mice bearing Le(Y)-positive tumors. We conducted a phase I study of 38 patients with solid tumors who failed conventional therapy and whose tumors expressed the Le(Y) antigen. Objective antitumor activity was observed in 5 patients, 18 had stable disease, 15 progressed. A complete remission was observed in a patient with metastatic breast cancer to supraclavicular nodes. A greater than 75% tumor reduction and resolution of all clinical symptoms lasting for more than six months was observed in a colon cancer patient with extensive retroperitoneal and cervical metastasis. Three patients (two colon, one breast cancer) had minor responses. The maximum tolerated dose of LMB-1 is 75 microgram/kg given intravenously three times every other day. The major toxicity is vascular leak syndrome manifested

by hypoalbuminemia, fluid retention, hypotension and, in one case, pulmonary edema. Although immunotoxins have been evaluated in clinical studies for more than two decades, this is the first report of antitumor activity in epithelial tumors.

L9 ANSWER 46 OF 53 MEDLINE
AN 95393219 MEDLINE
DN 95393219
TI A Trojan horse with a sweet tooth [news; comment].
CM Comment on: Nat Struct Biol 1995 Jun;2(6):466-71
AU Wilson I A; Stanfield R L
SO NATURE STRUCTURAL BIOLOGY, (1995 Jun) 2 (6) 433-6.
Journal code: B98. ISSN: 1072-8368.
CY United States
DT Commentary
News Announcement
LA English
FS Priority Journals
EM 199512

L9 ANSWER 47 OF 53 MEDLINE
AN 1999034978 MEDLINE
DN 99034978
TI Immunotoxins containing Pseudomonas exotoxin that target LeY damage human endothelial cells in an **antibody**-specific mode: relevance to vascular leak syndrome.
AU Kuan C T; Pai L H; Pastan I
CS Laboratory of Molecular Biology, Division of Basic Sciences, National Cancer Institute, NIH, Bethesda, Maryland 20892, USA.
SO CLINICAL CANCER RESEARCH, (1995 Dec) 1 (12) 1589-94.
Journal code: C2H. ISSN: 1078-0432.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199904
EW 19990402
AB Vascular leak syndrome (VLS) was originally found to be a major dose-limiting toxicity in humans with cancer treated with several immunotoxins (ITs) containing ricin A chain or blocked ricin. Recently, VLS has also been observed in patients treated with an IT containing the murine monoclonal **antibody** (MAb) B3 coupled to LysPE38, a recombinant truncated form of Pseudomonas exotoxin (PE) A. **Antibody** B3 (IgG1k) recognizes LewisY and related carbohydrate epitopes present on many human solid tumors, and B3-LysPE38 showed excellent antitumor activity in nude mice bearing tumors that express the B3 antigen. In the clinical trial, the development of VLS has prevented the administration of the amount of IT necessary to achieve blood levels required for good **therapeutic** responses. We have now investigated the effects of several PE-based ITs on different human endothelial cell lines to elucidate the mechanism of VLS induced by ITs containing PE. To assess the cytotoxic effect of IT on endothelial cells, various ITs were incubated with cells for 2 or 20 h, and the incorporation of [3H]leucine into protein was measured. The endothelial cells studied were human umbilical vein endothelial cells, human lung-derived microvascular endothelial cells (HUVECs), human adult dermal microvascular endothelial cells, human pulmonary artery endothelial cells, and human aortic endothelial cells. We found that both B3-LysPE38 (LMB-1), a chemical conjugate of MAb B3 with PE38, as well as B3(Fv)-PE38 (LMB-7), a recombinant single chain immunotoxin, inhibited protein synthesis, with 50% inhibitory concentrations between 600 and 1000 ng/ml for 20-h incubation in HUVECs, human lung-derived microvascular endothelial cells,

and human adult dermal microvascular endothelial cells but not on human pulmonary artery endothelial cells. The cytotoxic effect was specific since PE38 itself or PE coupled to several other **antibodies** did not inhibit protein synthesis in these cells even at 10,000 ng/ml. Further evidence that the cytotoxicity of B3-containing ITs is due to specific B3 binding to endothelial cells comes from the fact that the cytotoxicity can be blocked by excess free MAb B3. HUVECs undergo overt morphological changes after treatment with B3-LysPE38 or B3(Fv)PE38. Gaps between the cells are formed after a 20-h exposure but not after 2 h. These studies suggest that VLS in patients is due to capillary damage caused by prolonged exposure to high concentrations of LMB-1.

L9 ANSWER 48 OF 53 MEDLINE
AN 1999034973 MEDLINE
DN 99034973
TI Efficacy of compartmental administration of immunotoxin LMB-1 (B3-LysPE38) in a rat model of carcinomatous meningitis.
AU Bigner D D; Archer G E; McLendon R E; Friedman H S; Fuchs H E; Pai L H; Herndon J E 2nd; Pastan I H
CS Department of Pathology, Duke University Medical Center, Durham, North Carolina 27710, USA.
NC NS 20023 (NINDS)
CA 56115 (NCI)
CA 11898 (NCI)
SO CLINICAL CANCER RESEARCH, (1995 Dec) 1 (12) 1545-55.
Journal code: C2H. ISSN: 1078-0432.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199904
EW 19990402
AB LMB-1 (B3-LysPE38) is an immunotoxin composed of the tumor-reactive monoclonal **antibody** B3 and a genetically engineered form of Pseudomonas exotoxin. Monoclonal **antibody** B3 reacts with a carbohydrate epitope that is found on a number of solid tumors (e.g., breast, ovarian, and lung carcinomas) that frequently invade the intrathecal space, causing neoplastic meningitis. The Pseudomonas exotoxin has been engineered to remove the binding domain to eliminate nonspecific binding. A model of human neoplastic meningitis using rats bearing the human epidermoid carcinoma A431 was used for **therapeutic** studies of immunotoxin LMB-1. Therapy was initiated 3 days after injection of the tumor cells, which was one third of the median survival time of untreated rats. A single intrathecal injection of 40 microgram increased median survival from 9 days with saline injection to 16 days (78%, $P < 0.001$), and a single dose of 200 microgram increased median survival to 25 days (188%, $P < 0.001$). Three doses of 40 or 200 microgram given on days 3, 6, and 8 significantly increased the median survival of 9.5 days associated with saline injection to 40.5 days (326% increase) and 33.0 days (247% increase), respectively, with two long-term survivors (191-day survival) in each treatment group. LMB-1 had no **therapeutic** effect on the treatment of two B3 antigen-negative neoplastic meningitis models. Treatment of the antigen-positive A431 neoplastic meningitis with B3 alone or a nonspecific monoclonal, MOPC, coupled to the engineered Pseudomonas exotoxin produced no survival effects. Nontumor-bearing athymic rats showed no toxicity with a single dose of either 40 microgram or 200 microgram, or 3 doses of 40 microgram. However, when they were given three

doses of 200 microgram, these rats showed weight loss and loss of neurological function, and two of eight animals died. These studies indicate that, in the range of the most therapeutically effective dosage, the immunotoxin LMB-1 is tolerated in the intrathecal space and should be considered for human intrathecal trials.

L9 ANSWER 49 OF 53 MEDLINE
AN 95393226 MEDLINE
DN 95393226
TI The x-ray structure of an anti-tumour **antibody** in complex with antigen [see comments].
CM Comment in: Nat Struct Biol 1995 Jun;2(6):433-6
AU Jeffrey P D; Bajorath J; Chang C Y; Yelton D; Hellstrom I; Hellstrom K E; Sheriff S
CS Bristol-Myers Squibb Pharmaceutical Research Institute, Princeton, New Jersey 08543-4000, USA..
SO NATURE STRUCTURAL BIOLOGY, (1995 Jun) 2 (6) 466-71.
Journal code: B98. ISSN: 1072-8368.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199512
AB The crystal structures of the murine BR96 Fab and its human chimera have been determined in complex with the nonoate methyl ester derivative of Lewis Y (nLey) at 2.8 A and 2.5 A resolution, respectively. BR96 binds the carbohydrate in a large pocket which is formed by residues of all CDR loops except L2. The binding of the carbohydrate is mediated predominantly by aromatic residues in BR96. Analysis of the structure suggests that BR96 is capable of recognizing a structure larger than the Le(y) tetrasaccharide, providing a possible explanation for its high tumour selectivity. The structure provides a rationale for mutagenesis experiments that have resulted in BR96 CDR loop mutants with increased affinity for nLey and/or tumour cells.

L9 ANSWER 50 OF 53 MEDLINE
AN 96160043 MEDLINE
DN 96160043
TI Targeted therapy of carcinomas using BR96 sFv-PE40, a single-chain immunotoxin that binds to the Le(y) antigen.
AU Siegall C B
CS Molecular Immunology Department, Bristol-Myers Squibb, Pharmaceutical Research Institute, Seattle, WA 98121, USA.
SO SEMINARS IN CANCER BIOLOGY, (1995 Oct) 6 (5) 289-95. Ref: 44
Journal code: A6Y. ISSN: 1044-579X.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS Priority Journals
EM 199605
AB Monoclonal **antibody** BR96 recognizes a Le(y)-related carbohydrate antigen expressed on a wide range of carcinomas. Immunotoxins composed of BR96 and a binding defective form of Pseudomonas exotoxin A were constructed both as chemical conjugates and as fusion proteins. While both forms of BR96 immunotoxin were equally cytotoxic to human carcinoma cell lines in vitro, the fusion protein form, BR96 sFv-PE40, was > 10-fold more active in vivo as an antitumor agent. BR96 sFv-PE40 was used to target

established human tumor xenografts in both mice and in rats. The rat which displays the Le(y) antigen on the same normal tissues as humans appears to be an appropriate model for the preclinical evaluation of this immunotoxin. Complete regressions of lung, breast and bladder carcinomas were obtained in these models upon administration of well-tolerated doses of BR96 sFv-PE40. The clinical limitations of BR96 sFv-PE40, as well as other immunotoxins, depend on the management and/or prevention of neutralizing anti-immunotoxin **antibodies** and the onset of toxicities, specifically vascular leak syndrome.

L9 ANSWER 51 OF 53 USPATFULL
AN 93:74195 USPATFULL
TI Mouse monoclonal **antibodies** specific for normal primate tissue, malignant human cultural cell lines human tumors
IN Pastan, Ira, Potomac, MD, United States
Willingham, Mark C., Bethesda, MD, United States
PA The United States of America as represented by the Department of Health and Human Services, Bethesda, MD, United States (U.S. government)
PI US 5242813 19930907
AI US 1990-596289 19901012 (7)
DT Utility
EXNAM Primary Examiner: Lacey, David L.; Assistant Examiner: Adams, Donald E.
LREP Townsend and Townsend Khourie and Crew
CLMN Number of Claims: 8
ECL Exemplary Claim: 1
DRWN 1 Drawing Figure(s); 1 Drawing Page(s)
LN.CNT 569
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The subject invention relates to monoclonal **antibodies** and uses thereof. In particular, the invention relates to three monoclonal **antibodies**, referred to as B1, B3, and B5, which are useful in the treatment and diagnosis of many forms of cancer.

L9 ANSWER 52 OF 53 WPIDS COPYRIGHT 2001 DERWENT INFORMATION LTD
AN 1993-060580 [08] WPIDS
DNC C1993-027027
TI Human-mouse chimeric monoclonal **antibodies** - recognise di fucosyl Lewis blood group antigens Y-6 and B-7-2, useful for treating cancer and HIV infection.
DC B04 D16
IN CO, M S; LOIBNER, H
PA (COMS-I) CO M S; (SANO) SANDOZ LTD; (SANO) SANDOZ PATENT GMBH; (SANO) SANDOZ-ERFINDUNGEN VERW GES MBH; (NOVS) NOVARTIS AG; (NOVS) NOVARTIS-ERFINDUNGEN VERW GES MBH; (SANO) SANDOZ AG
CYC 19
PI EP 528767 A1 19930224 (199308)* EN 65p
R: AT BE CH DE DK ES FR GB GR IE IT LI LU NL PT SE
CA 2076432 A 19930222 (199319)
JP 05336989 A 19931221 (199404) 35p
US 5562903 A 19961008 (199646) 68p
EP 528767 B1 20000112 (200008) EN
R: AT BE CH DE DK ES FR GB GR IE IT LI LU NL PT SE
DE 69230545 E 20000217 (200016)
ES 2145004 T3 20000701 (200036)
ADT EP 528767 A1 EP 1992-810633 19920818; CA 2076432 A CA 1992-2076432 19920819; JP 05336989 A JP 1992-221361 19920820; US 5562903 A Cont of US 1992-932180 19920819, US 1993-53171 19930422; EP 528767 B1 EP 1992-810633 19920818; DE 69230545 E DE 1992-630545 19920818, EP 1992-810633 19920818; ES 2145004 T3 EP 1992-810633 19920818
FDT DE 69230545 E Based on EP 528767; ES 2145004 T3 Based on EP 528767
PRAI GB 1991-18013 19910821; GB 1992-4514 19920302
AB EP 528767 A UPAB: 19931119

The following are claimed: (A) human/mouse chimeric monoclonal **antibodies** (MABs) recognising the difucosyl Lewis blood gp. antigens Y-6 and B-7-2; (B) human/mouse chimeric MABs contg. the variable region of the murine **antibodies** BT55-2 and the constant region of human immunoglobulin heavy and light chains; (C) humanised **antibodies** recognising the difucosyl Lewis blood gp. antigens Y-6 and B-7-2; (D) humanised MABs contg. only the minimum necessary parts of the parent mouse **antibody** BR5-2 (E) a process for the prepn. of human/mouse chimeric MABs contg. the variable region of murine **antibodies** BR55-2 and the constant region of human immunoglobulin heavy and light chains; and (F) a process for the prepn. of humanised MABs contg. only the minimum necessary parts of the parent mouse **antibody** BR55-2.

USE/ADVANTAGE - The MABs recognise the difusosyl Lewis blood gp. antigens Y-6 and B-7-2 as for the parent BR55-2 MABs but do not induce the same human anti-mouse **antibody** response. Since the MABs show a restricted binding specificity associated with a lack of cross-reactivity to related antigens expressed on blood cells, eg. erythrocytes, they are particularly suited for **therapeutic** use in humans. The MABs are useful in the diagnosis and treatment of cancer of epithelial origin, e.g. breast, colorectal, ovarian, prostate, pancreatic or gastric cancer and small cell lung cancer. the MABs are also useful for immunotherapy of HIV infections since the **Lewis Y antigen** is also selectively expressed on HIV infected cells.

Dwg.0/42

L9 ANSWER 53 OF 53 WPIDS COPYRIGHT 2001 DERWENT INFORMATION LTD
AN 1992-057976 [08] WPIDS
DNC C1992-026159
TI Use of BR-55-2 **antibody** in HIV therapy - can be used alone or for targetting cytotoxic agents to infected cells.
DC B04 D16
IN LOIBNER, H
PA (SANO) SANDOZ LTD; (SANO) SANDOZ PATENT GMBH; (SANO) SANDOZ-PATENT-GMBH; (SANO) SANDOZ SA
CYC 23
PI DE 4025499 A 19920213 (199208)*
WO 9203165 A 19920305 (199212) 23p
RW: AT CH DE DK ES GB GR LU NL SE
W: AU CA HU JP KR US
AU 9183932 A 19920317 (199226)
PT 98622 A 19920630 (199230)
ZA 9106313 A 19930428 (199323) 24p
EP 547079 A1 19930623 (199325) EN 23p
R: AT BE CH DE DK ES FR GB GR IT LI LU NL SE
HU 64238 T 19931228 (199405)
JP 06500771 W 19940127 (199409) 7p
TW 223019 A 19940501 (199423)
AU 657489 B 19950316 (199518)
EP 547079 B1 19960410 (199619) EN 13p
R: AT BE CH DE DK ES FR GB GR IT LI LU NL SE
DE 69118702 E 19960515 (199625)
ADT DE 4025499 A DE 1990-4025499 19900811; WO 9203165 A WO 1991-EP1510 19910808; AU 9183932 A AU 1991-83932 19910808, WO 1991-EP1510 19910808; PT 98622 A PT 1991-98622 19910809; ZA 9106313 A ZA 1991-6313 19910809; EP 547079 A1 EP 1991-914884 19910808, WO 1991-EP1510 19910808; HU 64238 T WO 1991-EP1510 19910808, HU 1993-349 19910808; JP 06500771 W JP 1991-514194 19910808, WO 1991-EP1510 19910808; TW 223019 A TW 1991-106337 19910812; AU 657489 B AU 1991-83932 19910808; EP 547079 B1 EP 1991-914884 19910808, WO

1991-EP1510 19910808; DE 69118702 E DE 1991-618702 19910808, EP 1991-914884 19910808, WO 1991-EP1510 19910808

FDT AU 9183932 A Based on WO 9203165; EP 547079 A1 Based on WO 9203165; HU 64238 T Based on WO 9203165; JP 06500771 W Based on WO 9203165; AU 657489 B Previous Publ. AU 9183932, Based on WO 9203165; EP 547079 B1 Based on WO 9203165; DE 69118702 E Based on EP 547079, Based on WO 9203165

PRAI DE 1990-4025499 19900811

AB DE 4025499 A UPAB: 19931006

The use of BR55-2 **antibody** (Ab), its deriv. fragments,or conjugates, for treating HIV infections is new.

Ab is of isotype IgG3 and is opt. used as F(ab')2 fragments.

To form a strong bond between Ab and a radionuclide, the former is derivatised to introduce a chelating gp. Typically, the Ab is reacted with the hydroxysuccinimide ester of DPTA (2 hr. at pH 8-8.2) then the protein components collected. Binding of metal to the chelating gp. is conventional.

USE/ADVANTAGE - BR55-2 are known for treatment of tumour since they bind to the **Lewis Y-antigen**, a carbohydrate expressed on tumour cells. The same antigen is expressed by HIV-infected peripheral lymphocytes of AIDS patients. Ab can be used (a) to activate human effector functions for direct selective destruction of HIV-infected cells or (b) as carriers for cytotoxic cpds., e.g ricin, cell toxins, synthetic cytotoxins or radionuclides. For large mammals good results are achieved by slow intravenous infusion (over 2-3 hr.) of 50-100 mg Ab per infusion, given every second day over 2 weeks.